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Multicenter, randomized, active comparator-controlled, double-blind, double-dummy, parallel group, dose-finding Phase 2 study to compare the safety of the oral FXIa inhibitor BAY 2433334 to apixaban in patients with atrial fibrillation

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Acronym: PACIFIC-AF

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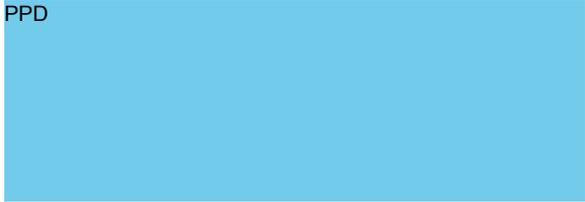
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Sponsor Signatory

PPD



PPD



Date

Medical Monitor (Study Medical Expert) name and contact information can be found in the Trial Master File (TMF)

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1. Protocol Summary

1.1 Synopsis

Protocol Title: Multicenter, randomized, active comparator-controlled, double-blind, double-dummy, parallel group, dose-finding Phase 2 study to compare the safety of the oral FXIa inhibitor BAY 2433334 to apixaban in patients with atrial fibrillation

Short Title: **PACIFIC-AF - Phase 2 Program of AntiCoagulation via Inhibition of FXIa by the oral Compound BAY 2433334 – Atrial Fibrillation study**

Rationale: Current guidelines recommend long-term oral anticoagulant therapy such as non-Vitamin K oral anticoagulants (NOACs) or Vitamin K antagonists (VKAs) for patients with atrial fibrillation (AF). Despite better benefit-risk profile for NOACs when compared to VKAs, patients receiving NOACs continue to have a significant risk for developing strokes, systemic embolism and CV death. In addition, there is still a significant risk for major bleeding. The inhibition of FXIa is expected to not lead to a relevant increase in bleeding and especially major bleeding, while maintaining the efficacy benefit of NOACs.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> to evaluate that the oral FXIa inhibitor BAY 2433334 when compared to apixaban leads to a lower incidence of bleeding in participants with AF 	<p>Primary Safety Endpoint</p> <ul style="list-style-type: none"> composite of International Society on Thrombosis and Hemostasis (ISTH) major and clinically relevant non-major bleeding <p>Secondary Safety Endpoints</p> <ul style="list-style-type: none"> all bleeding ISTH major bleeding ISTH clinically relevant non-major bleeding ISTH minor bleeding

The primary safety **estimand** is the ratio of the proportions of the composite of ISTH major and clinically relevant non-major bleeding within 3 months comparing pooled doses of BAY 2433334 and comparator drug apixaban in adult participants with AF who have taken at least one dose of study medication of BAY 2433334 or comparator drug apixaban, while the participant is alive and exposed to study intervention.

The secondary safety **estimands** are defined following the same approach for the individual secondary endpoints, as done for the primary safety estimand.

Overall Design:

This is a multicenter, randomized, active comparator-controlled, double-blind, double-dummy, parallel-group dose-finding study.

The study population includes participants with AF documented by ECG evidence with:

- CHA₂DS₂-VASc score ≥ 2 if male or
CHA₂DS₂-VASc score ≥ 3 if female

- Indication for treatment with an oral anticoagulant in:
 - any participant currently not treated with an oral anticoagulant (e.g. treatment naïve) or alternatively,
 - participant on a NOAC in case of at least one bleeding risk feature (history of a prior bleed within the last 12 months requiring medical attention and / or moderate renal dysfunction with eGFR 30-50 ml/min and / or current clinically indicated antiplatelet therapy with acetylsalicylic acid [ASA] \leq 100 mg).

Participants will be screened and randomized within 14 days of screening.

Stratification will be based on whether participants received a NOAC before study start or were not treated with any oral anticoagulant.

If all information is available, participants can be randomized on the day of screening.

Disclosure Statement: This is a parallel group treatment study with 3 arms that is participant and investigator blinded.

Intervention Model: Parallel

Primary Purpose: Treatment

Number of Arms: 3 arms (2 investigational drug arms and 1 comparator arm)

Number of Participants:

Approximately 800 participants will be screened to achieve 750 evaluable participants for an estimated total of 250 evaluable participants per intervention group. More details are available in Section 9.2 Sample Size Determination.

Intervention Groups and Duration:

BAY 2433334 is the sponsor's study drug under investigation. Apixaban is the drug used as comparator. The following intervention groups are included in the study:

- BAY 2433334 50 mg
- BAY 2433334 20 mg
- Apixaban 5 mg or 2.5 mg, according to label

Study interventions duration and dose regimen are tabulated as follows:

Study Period	Duration	Dose and Frequency	Route of administration
Screening	2 weeks		Oral
Intervention	12 weeks	BAY 2433334 ^a 50 mg OD BAY 2433334 ^a 20 mg OD Apixaban ^b 5 mg or 2.5 mg BID	
Safety follow-up	2 weeks		
Total planned number of participants	Total planned study duration (per participant)		
750	Between 14 and 16 weeks		

Abbreviations: BID = bis in die (twice a day), OD = once a day

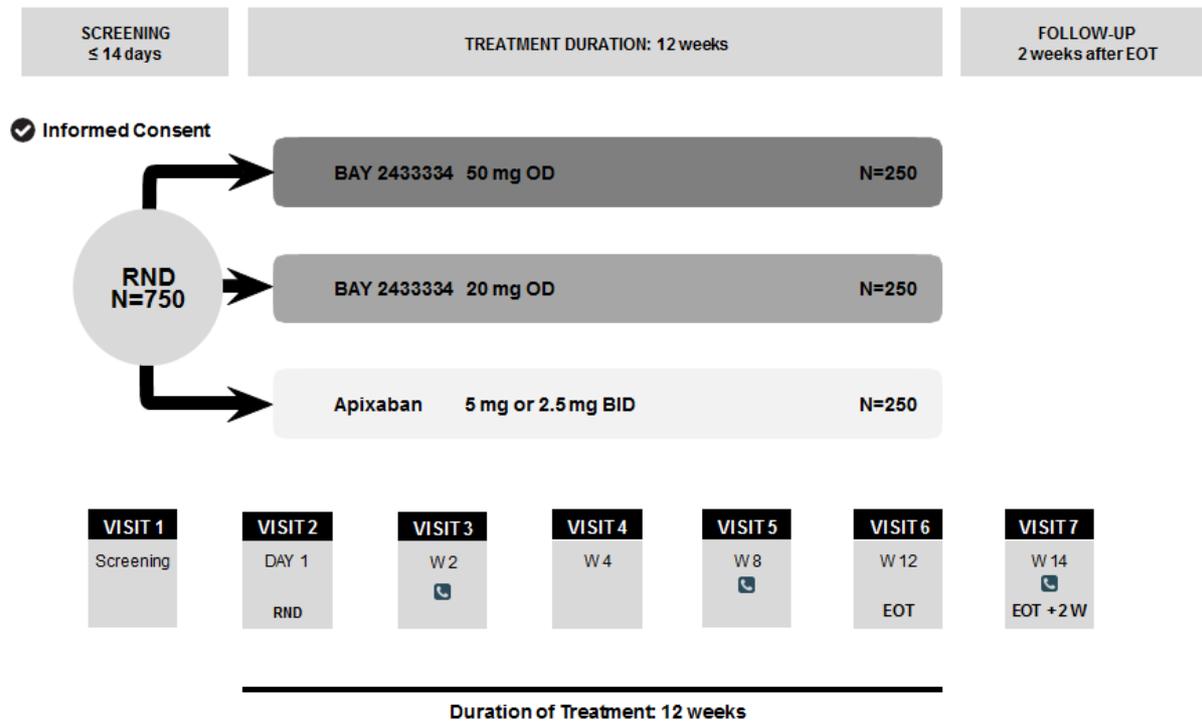
^a participants receiving BAY 2433334 will also receive the apixaban matching placebo

^b participants receiving apixaban will also receive the BAY 2433334 matching placebo

Data Monitoring Committee: Yes

1.2 Schema

Figure 1–1: Study design overview



Abbreviations: BID = bis in die (twice a day), EOT = End of Treatment, N = total number of participants, NOAC = Non-Vitamin K oral anticoagulant, OD = once a day, RND = randomization, W = week.
 Note: Participants receiving BAY 2433334 will also receive the apixaban matching placebo.
 Participants receiving apixaban will also receive the BAY 2433334 matching placebo.
 During the safety follow-up, further therapy (e.g. NOAC) is at discretion of the investigator.

1.3 Schedule of Activities (SoA)

Study periods (Duration)	Screening (SCR) (up to 2 weeks before RND)	Intervention period (12 weeks, from BL until EOT visit / ET visit ^a)						Safety Follow-up (SFU) (14 days after EOT or ET ^a)
		2	3	4	5	6	6a	
Visit number	1	2	3	4	5	6	6a	7
Visit type	site	site	☎	site	☎	site	site	☎
Week [W] Study day and allowed deviations	SCR -14 → 1	RND / W0 1	W2 15±4	W4 29±4	W8 57±4	EOT / W12 85±4	ET / Any time ET+7	W14 / ET+2Ws 99+7 / (ET+14)+7 ^a
Administrative procedures								
Signed informed consent	X							
Pharmacogenetic consent	X							
Dispense study contact card	X							
Inclusion and exclusion criteria	X	X ^b						
Demographics and biometrics	X							
Medical history	X	X ^b						
Prior ^c and concomitant medication	X	X ^b	X	X	X	X	X	X
Clinical procedures / assessments								
12-lead ECG ^d	X	X ^b				X	X	
Vital signs (BP and HR)	X	X ^b		X		X	X	
Outcome events ^e		←=====continuously=====→						
Adverse events		←=====continuously=====→						
IxRS								
Visit registration / randomization via IxRS	X	X						
Laboratory assessments								
Safety blood sample	X ^{b, f}	X ^f		X		X	X	
Pharmacokinetic sampling ^g				X		X	X	
Pharmacodynamic sampling ^g		X		X		X	X	
Pharmacogenetic sample ^g		X						
Biomarker sample ^g		X				X	X	
Study drug ^h administration								
Study drug ^h dispensation		X ⁱ						
Study drug ^h intake at the site ^g		X		X		no intake		
Study drug ^h collection and accountability						X	X	

Abbreviations: BP = blood pressure, BL = baseline, CRF = case report form, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, EOT = end of treatment, ET = early termination, HR = heart rate, IxRS = Interactive Voice/Web Response System, PD = pharmacodynamic(s), PK = pharmacokinetic(s), RND = randomization, SCR = screening, SFU = safety follow-up, SoA = Schedule of Activities, W = week

- ^a early termination visit is only applicable to participants who prematurely discontinue intake of study drug; such participants should undergo the ET visit as soon as possible after permanent discontinuation of study drug. A safety follow up visit will occur 2 weeks (+ 7 days window) after the day of the premature discontinuation of study drug (Section 7.1)
- ^b in case screening and randomization are performed on the same day, this procedure does not need to be repeated; **CAVE:** refer to footnote ^c
- ^c in case a participant pretreated with NOAC (or treated with another non-oral anticoagulant) has already taken the anticoagulant on the planned day of randomization, randomization should be postponed by one day (Section 6.1.1)
- ^d ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals should be used
- ^e outcome events including all bleeding, death, MI and stroke as well as events indicative of a potential outcome (Section 10.1.5.4) need to be reported on dedicated forms in the eCRF on an ongoing basis, even if the participant is permanently discontinued from study treatment
- ^f creatinine and eGFR values, as well as current AST and ALT values, must be available at randomization; if they are not available from screening central lab, the respective values should be determined in local laboratories prior to randomization
- ^g refer to [Table 1–1](#)
- ^h “Study drug” refers to “study intervention”, as defined in Section 6.1.
- ⁱ at each contact the participants should be instructed regarding study drug compliance.

PK, PD and Biomarkers sampling

An overview of the PK, PD and Biomarkers sampling is shown in [Table 1–1](#).

Table 1–1: PK, PD and Biomarker sampling

	Day 1 (Visit 2)	Week 4 ^a (Visit 4)				Week 12 ^b (Visit 6) / or ET
	Pre-dose Day 1	Pre-dose	0.5-1.5 h post-dose	2-4 h ^c post-dose	4-12 h ^c post-dose	Prior to dose ^d of open-label anticoagulant
PK ^e		X	X	X	X	X
PD ^e	X	X	X	X	X	X
Biomarkers Plasma	X					X
Biomarkers Serum	X					X
Genetics	X					

Abbreviations: ET = Early termination, PD = pharmacodynamic(s), PK = Pharmacokinetic(s)

^a at visit 4: in order to collect pre-dose samples for PK and PD, participants should take their study drug at the site only after blood sampling. The investigator must record the time when the study drug is taken at the site. A phone call to remind the participants is recommended

^b at visit 6: no study drug intake should take place on the day of this visit anymore. The last intake of study drug is occurring on the previous day. A phone call to remind the participants is recommended

^c the minimum time between the 2-4 h and the 4-12 h samples should be at least 1 hour

^d sampling should occur prior to the intake of an open-label anticoagulant that is supposed to be started instead of the blinded study drug after the end of the study drug treatment (refer to Section 6.1.1)

^e if study drugs will be temporarily stopped, PK / PD blood samples should only be obtained if the study drugs have been restarted and sustained for at least 4 days, see Section 7.1.1

The exact time of PK, PD and biomarker sampling needs to be recorded, as well as the time of the most recent / associated study drug intake (i.e. on the PK / PD sampling day, as well as on the day before that).

2. Introduction

BAY 2433334 is a direct, potent inhibitor of activated coagulation factor XI (FXIa) planned to be developed for 3 main indications:

1. Prevention of stroke and systemic embolism in patients with AF (cardioembolic stroke prevention)
2. Secondary stroke prevention in patients after an ischemic stroke (large artery, lacunar stroke, or embolic stroke of undetermined source [ESUS]) (non-cardioembolic stroke prevention)
3. Prevention of major adverse cardiac events (CV death, MI, stroke) in patients after an acute myocardial infarction (AMI)

Study 19765 will be a 3-month treatment duration Phase 2 study and will test BAY 2433334 against apixaban (NOAC), a FXa inhibitor, in participants with AF.

The current clinical development of BAY 2433334 (FXIa inhibitor) includes two additional Phase 2 studies in participants with non-cardioembolic ischemic stroke (study 19766) and in participants with AMI (study 20603). These two studies are planned to have a treatment duration of 6 to 12 months, testing BAY 2433334 against placebo on top of antiplatelet therapy.

Each individual study will have its own study objectives. However, in order to reach and draw conclusions concerning safety in general, and especially bleeding, the program is designed to pool the data across the three studies to help further characterize safety and efficacy.

2.1 Study Rationale

This Phase 2 study will explore two doses of BAY 2433334 in order to determine a lower risk for bleeding when compared to apixaban (a NOAC) as well as the dose that is safe and can be used in a Phase 3 study in the same indication.

Current treatment guidelines recommend the use of long-term oral anticoagulant therapy such as VKAs, or NOACs.

Despite a better benefit-risk profile for NOACs when compared to VKAs, patients receiving NOACs continue to have a significant risk for developing strokes, systemic embolism and CV death. In addition, even though NOACs lead to less intracranial hemorrhage compared to VKAs, there is still a significant risk for major and clinically relevant non-major bleeding.

BAY 2433334, as an oral FXIa inhibitor, is expected to show a benefit in reducing the risk for stroke in patients with AF in Phase 3. At the same time BAY 2433334 is expected to have a low bleeding risk. This is based on the available preclinical data, data from patients with inherited FXI deficiency and first clinical data from 2 Phase 2 proof-of-concept studies in participants undergoing total knee replacement (please see Section 2.3).

BAY 2433334 is therefore an attractive candidate to evaluate as a potential replacement for NOAC therapy in patients with AF.

2.2 Background

2.2.1 Disease background

AF is the most common sustained cardiac arrhythmia and is associated with increased rates of death, stroke and other thromboembolic events. It has been estimated that about 33.5 million patients worldwide are affected by AF. AF is a particularly common disorder in the elderly, with a prevalence of less than 1% in the population under 60 years of age, and with estimates of 17% among those over 80 years of age. As a consequence of the ageing population, the prevalence of AF is predicted to rise.

Patients who have AF are known to have an increased risk of stroke due to a predisposition to the development of atrial thrombi. Full anticoagulation with vitamin K antagonists was the recommended therapy until the introduction of NOACs.

2.2.2 Treatment Guidelines

Current guidelines AHA / ACC / HRS 2014 (January et al. 2014), as well as the focused update AHA / ACC / HRS 2019 (January et al. 2019), ESC 2016 (Kirchhof et al. 2016), and CHEST 2018 (Lip et al. 2018) recommend the use of long-term oral anticoagulant therapy such as VKAs or NOACs like Factor Xa - (rivaroxaban, apixaban, edoxaban) or Factor IIa - (dabigatran) inhibitors for patients with AF.

2.2.3 FXIa Inhibition: Mode of Action

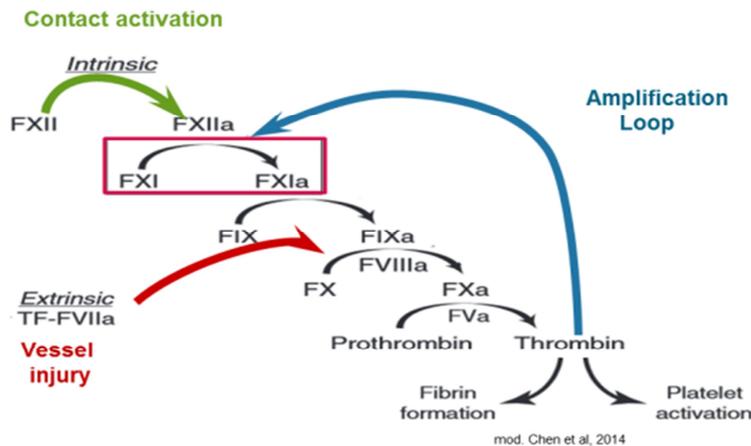
BAY 2433334 is a direct, potent inhibitor of activated coagulation factor XI (FXIa).

The plasma serine protease zymogen factor XI (FXI) is activated after initiation of the contact activation pathway via factor XIIa (FXIIa) and during the amplification Phase as part of a

positive feedback loop through activation by thrombin. FXIa is thought to contribute strongly to clot progression, which may potentially lead to vessel occlusion and pathological manifestations of thrombosis but has minor impact on hemostasis due to its limited role in the initiation Phase of the extrinsic pathway.

FXIa inhibition by BAY 2433334 may offer the opportunity to prevent thrombosis without interference with primary hemostasis and to thereby set a paradigm shift compared to Vitamin K antagonists and Non-Vitamin K oral anticoagulants (NOACs).

Figure 2–1: Contact activation



Source: adapted from (Chen et al. 2014)

2.2.4 BAY 2433334

2.2.4.1 Preclinical / Toxicology Data

Preclinical data using FXI-deficient mice or studies using pharmacological inhibition of FXIa in different animal models, for example a FeCl-induced thrombosis model, have shown a benefit in reduced thrombus formation. The data indicate that higher efficacy might be possible to achieve when compared to the therapeutic doses of NOACs.

The benefit in these animal models was not associated with an increase in bleeding time as is seen for NOACs in these models. Importantly, no further increase in bleeding time was seen even when BAY 2433334 was given on top of dual antiplatelet therapy.

Data regarding toxicology studies as well as more preclinical data can be found in the Investigator's Brochure but are also partly described in the benefit / risk section (see Section 2.3).

2.2.4.2 Clinical Data

So far, 156 healthy male subjects have received treatment with BAY 2433334 in doses ranging from 5 mg to 150 mg after single dosing and up to 100 mg once daily in multiple dose settings.

Safety

The single dose escalation study (study 19372) with BAY 2433334 is clinically completed. Single doses of 5 mg to 150 mg have been investigated, as well as a food effect study part with 25 mg. No clinically relevant signs or symptoms of bleeding were observed.

The multiple dose escalation study (study 19665) has also been clinically completed and evaluation is still ongoing. Therefore, the results are preliminary. It consisted of 3 parts: part A, wherein 25 mg, 50 mg and 100 mg BAY 2433334 were given once daily over 9 consecutive days; part B, where 25 mg were given twice daily; and part C, where a midazolam interaction was investigated with 25 mg and 75 mg BAY 2433334.

Overall, BAY 2433334 was safe and well tolerated. More details on safety can be found in the Investigator's Brochure.

Pharmacodynamics

The following pharmacodynamic parameters were investigated in both the FiM study (study 19372) and MDE study (study 19665): aPTT, FXI activity (AXIA assay), and FXI concentration. Bleeding time was investigated after single dose administration only (study 19372).

A dose dependent prolongation of aPTT was observed after single dosing with a close direct correlation between aPTT and plasma concentration:

- In the 25 mg OD dose step of the multiple dose (MD) study 19665 a prolongation of aPTT of ~50% (mean, compared to baseline) after single dosing and ~65% (mean) at steady state was seen.
- In the 50 mg OD dose step of the MD study 19665 a prolongation of aPTT of ~75% (mean, compared to baseline) after single dosing and ~105% (mean) at steady state was seen.
- In the 100 mg OD dose step of the MD study 19665 a prolongation of aPTT of ~85% (mean, compared to baseline) after single dosing and ~120% (mean) at steady state was seen.

FXI activity (AXIA assay) is inhibited by a mean of ~85% after 25 mg single dose (SD) and a mean of ~95% (25 mg OD) at steady state. After 50 mg and 100 mg SD and MD, activated FXI activity is inhibited by a mean of > 95% both after first dose and at steady state. The duration of the inhibition of FXI activity (AXIA assay) is dose dependent. Complete inhibition was reported for 12 hours for 50 mg at steady state and this is prolonged up to 24 hours for 100 mg at steady state.

Pharmacodynamic parameters aPTT and FXI activity correlated well with observed plasma concentrations of BAY 2433334.

No relevant changes of FXI concentration or PT were observed in either study.

No clinically relevant changes in bleeding time were observed after single dose application.

Pharmacokinetics

The key pharmacokinetics features of BAY 2433334 based on current available data and when administered as IR tablets can be summarized as follows.

- BAY 2433334 is absorbed with a median time to reach maximum plasma concentration (t_{max}) of 2 to 4 hours (fasted state).

- There is no hint for any deviation from dose-proportionality found for doses between 5 mg and 150 mg.
- Relative bioavailability of BAY 2433334 administered as IR tablet amounted to approximately 89.5% with regard to AUC and of 86.0% with regard to C_{max} , compared as oral solution
- A high-fat, high-calorie meal has minor effect on the AUC of 25 mg BAY 2433334 (decrease of 12.4%) and results in a reduced absorption rate (31.4% decrease in maximum plasma concentration [C_{max}] and 2.5 h prolongation in t_{max}).
- The variability was low to moderate for AUC and C_{max} (%*geoCV* approx. 15 to 30%).
- The degree of accumulation of BAY 2433334 is low regarding $C_{max,md}$ or $AUC_{\tau,md}$ after once daily multiple dosing with $R_A C_{max}$ between 1.4 and 1.6 and $R_A AUC$ between 1.5 and 1.7.
- Pharmacokinetics were linear over time.
- The metabolite M-10 (BAY 2826102, formed by amide hydrolysis of the central amide and subsequent *N*-acetylation) is expected to be a main compound in human plasma with a metabolic ratio to parent drug of approx. 24 to 37%. This metabolite is not pharmacologically active.
- Terminal half-life is 14.5 to 16.0 hours supporting once daily dosing.
- Low apparent oral plasma clearance (CL/F) of about 3.19-4.27 L/h was observed in geometric mean (corresponding to a blood clearance/ F of 4.54-6.07 L/h).
- Based on preliminary evaluation of the 50 mg dose step in the multiple dose escalation study (study 19665) renal elimination was low (15%).
- Based on the preliminary ethnic evaluation up to the 50 mg dose step of single and multiple dose in Caucasians (study 19665) and Japanese (study 19667), there is no large difference in PK between races though geometric mean of AUC and C_{max} in Japanese were slightly higher than in Caucasians.
- Based on preliminary evaluation the strong CYP3A4 inhibitor itraconazole increased BAY 2433334 exposure by 100% (2-fold) while maximum plasma concentrations were not changed (study 19664). Terminal half-life was prolonged from 16 to 29 hours.

More details can be found in the Investigator's Brochure.

2.3 Benefit / Risk Assessment

The FXIa inhibitor BAY 2433334 is an oral anticoagulant that is planned to be developed for patients with AF, acute myocardial infarction as well as non-cardioembolic ischemic stroke. This Phase 2 study will be the first study investigating BAY 2433334 in patients with AF. Once daily doses of 20 mg and 50 mg will be tested in the study.

BAY 2433334 as an FXIa inhibitor is expected to have a lower risk for clinically significant bleeding when compared to other oral anticoagulants (VKAs and NOACs), while leading to an efficacy benefit.

The expected clinical profile of BAY 2433334 is based on preclinical data as well as clinical data from FXI-deficient individuals and other FXI-targeting compounds. The separation of bleeding and efficacy might be explained by the fact that inhibition of FXIa affects the

intrinsic and propagation pathways, but keeps the extrinsic pathway unaffected, which is activated in case of vessel injury.

At this stage of development there is no clinical evidence available yet to confirm the efficacy benefit of BAY 2433334. However, the data supporting that this compound is expected to lead to prevention of thrombosis events in the intended indications are the following:

- FXI-deficient knockout mice are protected from thrombosis. In addition, in various thrombosis models in rabbits, BAY 2433334 demonstrated reduced thrombus weight, and this was seen when given with or without antiplatelets. While therapeutic doses of NOACs lead to a 20-30% reduction in thrombus formation in the same animal models, BAY 2433334 was able to reduce the thrombus formation by up to ~90%.
- In people with inherited Factor XI deficiency, a rare coagulation deficiency caused by either reduced production of factor XI or by production of a loss-of-function factor XI molecule, a lower risk for venous thromboembolic events as well as cardiovascular events and especially stroke has been reported.
- Increased levels of FXI are reported as a risk factor for venous thromboembolism and myocardial ischemia or stroke. Whether there is a causal relationship is unclear.
- A first proof of concept targeting FXI as anticoagulant has been shown by an FXI Antisense Oligonucleotide. Reducing FXI levels in patients undergoing total knee arthroplasty (TKA) led to an improved prevention of postoperative venous thromboembolism (VTE), when compared to enoxaparin. Based on modeling approaches, the inhibition levels of FXIa activity in the study can be achieved with the 20 mg and 50 mg doses of BAY 2433334 (see also the Investigator's Brochure).
- Phase 1 studies in healthy volunteers are not able to assess efficacy. However, after multiple dosing the highest planned dose of 50 mg to be tested in Phase 2 lead to inhibition of FXI activity by a mean of >95% and complete inhibition during 12 hours of the day. This was combined with a mean prolongation of aPTT of ~105%.

At this stage of development, the safety profile has not been established. The following information related to safety, as well as potential risks for participants, is available:

1. Bleeding is the main safety concern related to antithrombotic therapies. For an inhibitor of FXIa a lower bleeding risk is expected. Data supporting this are listed below:
 - FXI-deficient knockout mice do not show a bleeding phenotype. In addition, in the thrombosis animal models no increase in bleeding time (gum and ear) was reported. Importantly, no further increase in bleeding time was seen when BAY 2433334 was given on top of dual antiplatelet. In addition, in the toxicology studies no relevant bleeding was reported for up to 37-fold the expected human exposure of the planned 50 mg multiple dose in participants.
 - Patients with inherited FXI deficiency are typically identified when presenting with a prolonged activated partial thromboplastin time (aPTT) in routine clinical testing. There is no direct association between FXI activity levels and bleeding risk, though historically and predominantly in the Ashkenazi Jewish population, FXI deficiency has been categorized as having a mild bleeding phenotype that generally only manifests following injury or trauma in tissues with high fibrinolytic activity.

- In the completed and ongoing Phase 1 studies conducted with BAY 2433334, no relevant bleeding events were reported so far.

A risk for bleeding cannot be excluded in participants with AF included in the Phase 2 study. Therefore, bleeding will be closely monitored in the study and will be adjudicated by an independent clinical event committee.

2. In toxicology studies, the liver was identified as a target organ in the rat but not in the dog. This included dose-dependent spontaneous, mostly transient increases in liver enzymes in single animals without clear correlation to histopathological findings in the liver. Based on this, participants with a > 2.5 ALT or AST increase will be excluded from the study and liver findings during the study will be monitored and are defined as AE of special interest in the study.
3. Single doses of BAY 2433334 up to 150 mg and multiple doses up to 100 mg once daily for 9 days have been safe and well tolerated. This included general safety, laboratory, vital signs and ECGs. The doses were 2 and 3-fold higher than planned in this Phase 2 study.
4. Based on preliminary evaluation the strong CYP3A4 inhibitor itraconazole increased BAY 2433334 exposure by 100% (2-fold) while maximum plasma concentrations were not changed (study 19664). Terminal half-life was prolonged from 16 to 29 hours. Therefore, strong CYP3A4 inhibitors and inducers should not be taken concomitantly with BAY 2433334 in this study until further information is available.

Participants assigned to BAY 2433334 will not receive standard of care. In order to address the potential risk for stroke in case of undertreatment, the study design follows the recommendation from the European Guideline and limits the treatment duration to 3 months. During this period the general risk for stroke should be < 1%. In addition, the study investigates only the 2 higher doses of 20 mg and 50 mg and not the lower dose of 10 mg, which will be tested only in the 2 placebo-controlled studies in participants after an acute myocardial infarction or non-cardioembolic ischemic stroke. 20 mg and 50 mg as the selected doses will provide significant FXIa inhibition over the 24-hour period > 60% at trough and mean > 75%. Based on preclinical data these inhibition levels should lead to an even higher anticoagulant effect than reached with available anticoagulants.

In order to ensure the safety of the participants during the study conduct an independent data monitoring committee (IDMC) will monitor the safety of all participants enrolled in all 3 Phase 2 studies with a focus on bleeding and general safety. In addition, a focus of the IDMC review will be on any stroke occurring during the study.

Several Factor XI (FXI) and activated Factor XI (FXIa) inhibitor assets are currently in development as antithrombotics, including antisense oligonucleotides (ASOs), antibodies and small molecules (SMOLs).

In summary, in this Phase 2 study participants with AF will receive for the first time BAY 2433334. The main objective of the study is to explore that BAY 2433334 will lead to less bleeding when compared to a NOAC (apixaban). An additional objective is to guide dose selection for Phase 3. Currently, available preclinical and clinical data from the ongoing studies regarding the key risks do not indicate an unfavorable risk profile for BAY 2433334. The overall risk is anticipated to be acceptable in the context of the drug benefit. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BAY 2433334 may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Objectives and endpoints (primary, secondary and exploratory) of the study are reported below, in [Table 3–1](#). Please refer to Section [9.4](#) for further details.

Table 3–1: Objectives and Endpoints

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> to evaluate that the oral FXIa inhibitor BAY 2433334 when compared to apixaban leads to a lower incidence of bleeding in participants with AF 	<p>Primary Safety Endpoints</p> <ul style="list-style-type: none"> composite of ISTH major and clinically relevant non-major bleeding <p>Secondary Safety Endpoints</p> <ul style="list-style-type: none"> all bleeding ISTH major bleeding ISTH clinically relevant non-major bleeding ISTH minor bleeding <p>Exploratory Safety Endpoints</p> <ul style="list-style-type: none"> TIMI clinically significant bleeding TIMI major bleeding TIMI minor bleeding BARC bleeding definition type 2, 3, 5 BARC bleeding definition type 3, 5 BARC bleeding definition type 1, 2, 3, 5
Exploratory	
<ul style="list-style-type: none"> to explore the efficacy of BAY 2433334 compared to apixaban in reducing the risk for cardiovascular events (CV death, MI, stroke, systemic embolism) in participants with atrial fibrillation to explore additional pharmacokinetic and pharmacodynamic parameters, biomarkers and genetics to further investigate the study intervention (i.e. mode-of-action-related effects and/or safety) and to further investigate pathomechanisms deemed relevant to cardiovascular diseases and associated health problems 	<p>Exploratory Efficacy Endpoint</p> <ul style="list-style-type: none"> composite as well as individual components of CV death, MI, ischemic stroke, systemic embolism all-cause mortality <p>Other Exploratory Endpoints</p> <ul style="list-style-type: none"> FXIa inhibition, aPTT, D-Dimer Pharmacokinetics Various biomarkers (e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

Abbreviations: AF = atrial fibrillation, aPTT = activated partial thromboplastin time, BARC = Bleeding Academic Research Consortium, CV = cardiovascular, ISTH = International Society on Thrombosis and Hemostasis, MI = myocardial infarction, TIMI = thrombolysis in myocardial infarction

The primary safety **estimand** is the ratio of the proportions of the composite of ISTH major and clinically relevant non-major bleeding within 3 months comparing pooled doses of BAY 2433334 and comparator drug apixaban in adult participants with AF who have taken at least one dose of study medication of BAY 2433334 or comparator drug apixaban, while the participant is alive and exposed to study intervention.

The secondary safety **estimands** are defined following the same approach for the individual secondary endpoints as done for the primary safety estimand. Please also refer to Section [9.4](#) for further details.

4. Study Design

4.1 Overall Design

Study 19765 is a multicenter, randomized, active-comparator controlled, double-blind, double-dummy, parallel group, dose-finding Phase 2 study. The overall study design is depicted in [Figure 1–1](#).

Approximately 750 participants ≥ 45 years of age, from approximately 115 study centers worldwide will be randomized to 1 of the 3 arms (250 participants per arm): 2 investigational drug arms (BAY 2433334) and 1 active comparator arm (apixaban), in addition to their potential background therapy (for details see [Section 6.5](#)). Stratification will be based on whether participants received a NOAC before study start or were not treated with any oral anticoagulant.

The planned study duration will be 14-16 weeks, consisting of:

- **Screening period (visit 1 until visit 2):** 2 weeks (participants will be screened and have to be randomized within 2 weeks of screening. If all information is available, a participant can be randomized on the day of screening (visits 1 and 2 are combined).
- **Treatment period (from visit 2 through visit 6 [EOT] or visit 6a [ET]):** 12 weeks
- **Safety follow-up (visit 7 [SFU]):** 14 days (+ 7 days) after EOT or ET.

Study visits will take place as visits at the study sites and telephone calls. Visits at the study sites take place at screening and randomization (visit 1 and visit 2), at week 4 (visit 4) and week 12 (i.e. EOT, visit 6).

Telephone calls will take place at week 2 (visit 3), week 8 (visit 5), as well as 2 weeks after the EOT visit for participants who will take study intervention until the planned EOT (i.e. SFU, visit 7).

For participants who prematurely discontinue from study intervention, an early termination (ET) visit (visit 6a) will take place as soon as possible as visit at the study sites. Telephone calls take place 14 days after the ET visit (i.e. SFU, visit 7). Further details are reported in [Section 7.1](#).

Details of study procedures and their timing are summarized in the SoA.

4.2 Scientific Rationale for Study Design

The Phase 2 study in stroke prevention in AF will be a dose ranging study with the objective to identify the dose to be tested in Phase 3. The study aims at showing that the oral FXIa inhibitor BAY 2433334 when compared to apixaban (a NOAC, FXa inhibitor, 2.5 mg / 5 mg doses according to label) leads to a lower incidence of ISTH major and clinically relevant non-major bleeding. The Phase 2 study will not allow for an assessment of efficacy versus apixaban due to the limited number of efficacy events within a 3 months treatment period ($< 0.5\%$ at 3 months). The study is designed in line with the current European Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in participants with non-valvular atrial fibrillation ([EMA 2014](#)).

Study 19765 is a multicenter, randomized, active comparator-controlled, double-blind, double-dummy, parallel group, dose-finding Phase 2 study in 750 participants (250 participants per arm) with atrial fibrillation. The study will apply the principles of

randomization and double-blinding in order to prevent bias in the inclusion of participants or reporting of safety or efficacy events.

In addition, the study will follow a parallel group design in order to prevent bias in the data due to e.g. different sites in different countries enrolling at different timepoints into the study or in case of any seasonally related differences. There does not appear to be a requirement for a dose escalation approach, because based on the available preclinical and clinical data for BAY 2433334 there are no safety concerns related to the highest dose of 50 mg once daily tested in the study.

The study will include any participant who is not treated with on oral anticoagulant at study entry and includes e.g. participants newly diagnosed with AF and who are treatment-naïve. In addition, participants on a NOAC can be enrolled, but only if they have ≥ 1 additional bleeding risk feature, because participants on a NOAC are expected to have a significantly lower risk for bleeding when compared to untreated participants, as they were already exposed to an anticoagulant before. Participants on Vitamin K antagonists (VKA) are excluded from the study, as the switch from VKA to study drug may lead to bleeding events related to this switch and not to the assigned treatment.

4.3 Justification for Dose

The study will test the once daily doses of 20 mg (mid dose) and 50 mg (high dose) of BAY 2433334.

The selection of the high dose in this study was not limited by the safety and tolerability data from toxicology studies, nor from the results of the human Phase 1 studies conducted in healthy volunteers. Single doses up to 150 mg or multiple doses up to 100 mg for 9 days were tested in the Phase 1 studies. Due to these favorable results, the dose selection for the Phase 2 studies was primarily based on pharmacodynamic assays (preclinical and Phase 1 studies) including aPTT and FXIa activity.

Modeling approaches of the available Phase 1 data were used to predict the doses for Phase 2 studies with the goal to select doses that cover a broad range of inhibition of FXIa and lead to different degrees of increases in aPTT ([Table 4–1](#)).

- The high dose of 50 mg was chosen to reach significant inhibition of FXIa and to achieve maximum efficacy. However, this dose should not lead to a complete inhibition of FXIa during the majority of the day. The selected 50 mg dose is expected to lead to a mean FXIa activity of 7 % with FXIa activity < 10% during 14 hours of the day. aPTT is predicted to increase to 1.4 at trough and 1.9 at peak.
- The mid dose of 20 mg was selected as the second dose to reflect a dose linear response related to FXIa inhibition. This dose leads to a mean FXIa activity of 23%
- The low dose of 10 mg was not selected for this study, where BAY 2433334 is compared against standard of care, the NOAC apixaban. The rationale for this is to prevent participants from possible underdosing. This dose will be tested only in the placebo-controlled studies in participants after an acute myocardial infarction (study 20603) or non-cardioembolic ischemic stroke (study 19766). For 10 mg the expected mean FXIa activity is 45% and aPTT is increased to 1.1 at trough and 1.3 at peak.

Table 4–1: BAY 2433334: dose selection

Humans, multiple dose, modelled OD dosing	Predicted FXIa activity			Predicted aPTT increase	
	Trough %	Peak %	Mean %	Trough %	Peak %
50 mg	13	3	7	1.4	1.9
20 mg	40	11	23	1.2	1.5

Abbreviations: aPTT = activated partial thromboplastin time, OD = once a day

4.4 End of Study Definition

A participant is considered to have completed the study if he / she has completed all phases of the study including the last scheduled study visit.

The end of the study is defined as the date of the last visit of the last participant in the study globally.

5. Study Population

The study will enroll adult participants with non-valvular AF at moderate to high risk for future thromboembolic events and who therefore qualify for anticoagulant therapy.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Male and female participants are eligible to be included in the study only if all of the following criteria apply:

Age

- Participant must be 45 years of age or older at the time of signing the informed consent.

Type of Participant and Disease Characteristics

- Participant with AF documented by ECG evidence* with
 - CHA₂DS₂-VASc score ≥ 2 if male or
CHA₂DS₂-VASc score ≥ 3 if female
 - Indication for treatment with an oral anticoagulant in
 - any participant currently not treated with an oral anticoagulant (e.g. treatment naïve) or alternatively,
 - participant on a NOAC in case of at least one bleeding risk feature (history of a prior bleed within the last 12 months requiring medical attention and / or moderate renal dysfunction with eGFR 30-50 ml/min and / or current clinically indicated antiplatelet therapy with ASA ≤ 100 mg)

* AF should be either documented on the baseline 12-lead ECG, or otherwise within the last 12 months on a previous 12-lead ECG or an episode of AF of at least 30 seconds in case of continuous ECG recording, rhythm strip, pacemaker or implantable cardiac defibrillator interrogation

Informed Consent

3. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent has to be signed before any study procedure.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Mechanical heart valve prosthesis
2. Any degree of rheumatic mitral stenosis or moderate-to-severe, non-rheumatic mitral stenosis
3. Atrial fibrillation due to a reversible cause, participants in sinus rhythm after successful ablation, or plan for cardioversion or ablation during study conduct
4. Stroke within the last 30 days of screening
5. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) at randomization
6. Active bleeding; known bleeding disorder
7. Known significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or hepatic insufficiency classified as Child-Pugh B or C (see Section 10.6), or ALT/AST > 2.5 x the upper limit of normal, measured between screening and randomization
8. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², calculated by Modification of Diet in Renal Disease (MDRD) formula (see Section 10.7), determined between screening and randomization
9. Major surgery during the last 30 days or planned major surgery or intervention within study period (e.g. carotid endarterectomy, coronary artery bypass grafting)
10. Known allergy, intolerance or hypersensitivity to either of the study interventions (active substance or excipients)
11. Any contraindication for the use of an anticoagulant or listed in the local labeling for apixaban.

Prior / Concomitant Therapy

12. Requirement for chronic anticoagulation (for a different indication than AF e.g. mechanical heart valve or cardiac thrombus) or antiplatelet therapy (up to 100 mg ASA is allowed). Anticipated need for chronic (more than 4 weeks) therapy with NSAIDs
13. Treated with a Vitamin K antagonist in the 30 days prior to screening
14. Concomitant use of any of the following therapies within 14 days (or at least five half-lives of the active substance whatever is longer) before randomization and first study intervention administration (see Section 6.5):

- Strong inhibitors of cytochrome P450 isoenzyme 3A4 (CYP3A4) e.g. human immunodeficiency virus protease inhibitors, systemically used azole-antimycotic agents, clarithromycin or telithromycin
- Strong inducers of CYP3A4, e.g. phenytoin, carbamazepine, phenobarbital, rifampicin or St. John's wort.

Other exclusions

15. Known current alcohol and / or illicit drug abuse that may interfere with the participant's safety and / or compliance at the discretion of the investigator
16. Women of childbearing potential (women are considered of childbearing potential if they are not surgically sterile or postmenopausal, defined as amenorrhea for > 12 months). Male participants not willing to use condoms when sexually active with a woman of childbearing potential
17. Close affiliation with the investigational site or sponsor; e.g. a close relative of the investigator, or a dependent person (e.g. employee or student of the investigational site or the sponsor)
18. Previous (within 30 days or 5 half-lives of the investigational drug, whichever is longer) or concomitant participation in another clinical study with investigational medicinal product(s) or device(s). Registries and observational studies are allowed
19. Any condition or therapy, which would make the participant unsuitable for the study (e.g. non-compliance, dysphagia with inability to swallow study intervention) or otherwise vulnerable (e.g. participant in custody by order of an authority or a court) or life expectancy < 3 months.

5.3 Lifestyle Considerations

No restrictions during any of the study periods pertaining to lifestyle (except for the above-mentioned substance abuse) and/or diet apply.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Interventions Administered

The following study interventions will be administered in the study:

- BAY 2433334: sponsor's study drug under investigation
- Placebo to BAY 2433334
- Apixaban: marketed product used as comparator
- Placebo to apixaban

BAY 2433334 is supplied in various strengths as film-coated, immediate-release tablets with identical appearance. BAY 2433334 is taken orally once a day in the morning, preferably around the same time each day. The immediate-release tablets will be provided as pink, oval, film-coated tablets containing either 5 mg, 15 mg or 25 mg of BAY 2433334 (see [Table 6–1](#)).

Apixaban, the active comparator used in this study, is a selective, orally active inhibitor of the coagulation factor Xa (FXa) developed by Bristol-Myers Squibb (BMS) and Pfizer as an anticoagulant agent. It is supplied as 5 mg and 2.5 mg gelatin hard capsules with identical appearance. Apixaban is taken orally twice a day. The usual dose is 5 mg, reduced to 2.5 mg for participants with any 2 of the following criteria: age 80 years or older, body weight less than 60 kg, or serum creatinine level of 1.5 mg per dL or more. Participants have to receive the dose of apixaban according to the label and the respective dosage of apixaban for the entire duration of the study will be determined based on the values current at the randomization visit.

The study interventions (tablets and capsules) are not to be broken, halved or crushed, and should be swallowed whole with a glass of water. Both study interventions can be taken irrespective of food intake.

Matching placebos for both BAY 2433334 and apixaban are supplied in the same way.

For apixaban / placebo one capsule in the morning and one capsule in the evening are to be taken, and in addition for BAY 2433334 / placebo two tablets from two different bottles (one tablet from each bottle) are to be taken in the morning only.

Missed study intervention dose

The planned double-blind treatment phase starts at randomization and ends at or when study intervention is permanently discontinued. Study intervention intake will start as soon as possible after randomization (day 1) and is expected to continue through the end of the planned treatment.

If a dose of BAY 2433334 is missed, the participant should take a dose immediately on the same day.

If a dose of apixaban is missed, the dose should be taken as soon as possible on the same day and a twice daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

Table 6–1: Study Interventions

Arm name	BAY 2433334 high dose		BAY 2433334 medium dose		Apixaban	
	BAY 2433334	Placebo to apixaban	BAY 2433334	Placebo to apixaban	Apixaban	Placebo to BAY 2433334
Intervention Name	BAY 2433334	Placebo to apixaban	BAY 2433334	Placebo to apixaban	Apixaban	Placebo to BAY 2433334
Type	drug	placebo	drug	placebo	drug	placebo
Dose formulation	tablet	capsule	tablet	capsule	capsule	tablet
Unit dose strengths	25 mg	NA	5 mg and 15 mg	NA	2.5 mg or 5 mg	NA
Dosage Level(s)	50 mg	NA	20 mg	NA	2.5 mg or 5 mg	NA
Frequency	Once a day in the morning	Twice a day	Once a day in the morning	Twice a day	Twice a day	Once a day in the morning
Route of Administration	oral	oral	oral	oral	oral	oral
Use	experimental	placebo	experimental	placebo	active comparator	placebo
IMP/AxMP	IMP	IMP	IMP	IMP	IMP	IMP
Packaging and Labeling	HDPE bottles with desiccant capsule	blisters	HDPE bottles with desiccant capsule	blisters	blisters	HDPE bottles with desiccant capsule

Abbreviations: AxMP = auxiliary medicinal product, HDPE = high-density polyethylene, IMP = investigational medical product, NA = not applicable

All study interventions will be labelled according to the requirements of local regulations.

For all administered study interventions, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study intervention can be traced back to the respective bulk batch of the ingredients.

A complete record of batch numbers and expiry dates of all administered study interventions as well as the labels will be maintained in the sponsor's study file.

6.1.1 Switching to study intervention and back to open-label anticoagulant

As per inclusion criterion, when being enrolled, study participants may be treated with a NOAC or not treated with any oral anticoagulant. Hence participants treated with any VKA are not eligible.

After the participant is determined to be eligible for the study during the screening period, he or she should be instructed to discontinue any treatment with NOAC or any other non-oral anticoagulant, to allow that the last intake of the open-label NOAC (or non-oral anticoagulant) will occur on the day prior to randomization. Hence, a participant should not take open-label NOAC (or any other non-oral anticoagulant) on the day of the first dose of study intervention; if a participant has already taken his open-label NOAC (or other non-oral anticoagulant) on the planned day of randomization, randomization should be postponed by a day.

Transition from blinded study intervention to an open-label anticoagulant (NOAC or another recommended anticoagulant as deemed appropriate by the investigator) after final discontinuation of study intervention must be done without breaking the study blind. The

recommended procedure is to start with an open-label anticoagulant on the next day following the last day of intake of the blinded study inter (i.e. on the day of the end of treatment visit, as no study intervention intake should take place on the day of this visit anymore).

6.2 Preparation / Handling / Storage / Accountability

All study interventions will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor or its affiliates.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Site File.

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an Interactive Web Response System (IWRS). To accomplish random assignments, computer-generated randomization lists specified by the sponsor's responsible statistician will be prepared by Randomization Management at the study sponsor. The randomization lists are provided to an IWRS vendor. Before the study is initiated, the log in information & directions for the IWRS will be provided to each site.

The randomization will be stratified based on whether participants received a NOAC before study start or were not treated with any oral anticoagulant.

Study intervention will be dispensed at the study visit 2, as summarized in SoA.

Returned study intervention should not be re-dispensed to the participants.

Participants will be randomly assigned in a [1:1:1] ratio to receive study intervention.

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

Tablets containing 5 mg, 15 mg or 25 mg of BAY 2433334 and matching placebo are identical in appearance and packed in bottles labeled with a unique number which will be pre-printed on each bottle. Capsules containing apixaban and corresponding placebo are identical in appearance and packed in blisters labeled with a unique number which will be pre-printed on each blister. In order to achieve the double blind, double dummy design, participants will be provided with bottles and blisters either with active drugs (BAY 2433334 or apixaban), or placebo depending on the randomization outcome.

6.3.1 Unblinding

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a participant's treatment assignment is warranted. If the investigator is unavailable, and a treating physician not associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the study specific emergency medical advice 24 hours / 7-day service. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment, unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

BAY 2433334 is known to prolong the activated partial thromboplastin time (aPTT) in a dose dependent manner. aPTT is a commonly used functional coagulation test widely used in clinical practice in participants using anticoagulants and is as well commonly used during acute hospitalizations, and as pre-procedural screening test. Thus, inadvertent unblinding of the participant or investigator might take place in cases where aPTT test results are known. Therefore, the measurement of aPTT during the study conduct is strongly discouraged and should only be done in case of (emergency) situations where aPTT may help to guide treatment decision. aPTT determinations obtained as part of the study protocol will not be reported to investigators during the study in order to maintain the blinding.

6.4 Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit by direct questioning. At EOT (ET) visit, compliance will be assessed by counting returned tablets / capsules. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

To monitor compliance, the investigator will be required to document drug dispensing and return for each participant. Overall compliance with study intervention intake should be between 80% and 120% of the scheduled dose at the end of treatment with study intervention. The date of dispensing the study intervention to the participant will be documented. Study intervention will be dispensed according to the schedule provided in the SoA (Section 1.3). Participants should be instructed to bring all unused study intervention and empty packages at the EOT or ET visit for accountability purposes. Any discrepancies between actual and expected amount of returned study medication must be discussed with the participant at the time of the visit, and any explanation must be documented in the source records.

6.5 Concomitant Therapy

Any relevant medication or vaccine (including over-the-counter or prescription medicines, vitamins, and / or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor (sponsor's Study Medical Expert) should be contacted if there are any questions regarding concomitant or prior therapy.

Special focus needs to be on antiplatelet and anticoagulant medications, for which any change in 30 days before screening and concomitant use from study entry until the last scheduled study visit of the participant, needs to be captured on the specified concomitant medication page.

ASA, at doses of ≤ 100 grams/day, is permitted for use any time during the study. Higher doses of ASA and / or P2Y₁₂ inhibitors in combination with the study interventions are only allowed in the exceptional case of an acute myocardial infarction and / or after PCI that occurs during the study. Such treatment may be administered as per discretion of the investigator, after thorough assessment of the risk / benefit ratio of such a potential triple therapy approach.

The concomitant use of NSAID therapy during the study is strongly discouraged since this has been shown to increase the risk of gastrointestinal (GI) bleeding. However, if a NSAID must be temporarily used, it is recommended that the lowest possible dosage for the shortest duration possible is selected, not to exceed 4 weeks. Should analgesics be needed, use of paracetamol / acetaminophen is recommended.

Concomitant therapy with any of the following drugs is prohibited from 14 days (or at least five half-lives of the active substance, whatever is longer) before first study intervention administration, until at least 48 hours after last study intervention administration:

- Strong inhibitors of cytochrome P450 isoenzyme 3A4 (CYP3A4) e.g. human immunodeficiency virus protease inhibitors (ritonavir, indinavir, nelfinavir, atazanavir, or saquinavir), systemically used azole antimycotic agents (ketoconazole, itraconazole, voriconazole, or posaconazole), clarithromycin, telithromycin
- Strong inducers of CYP3A4, e.g. phenytoin, carbamazepine, phenobarbital, rifampicin, or St. John's wort

A separate complete list with prohibited medications will be provided to the investigator.

6.5.1 Guidance for Management of Participants who Have Bleeding During the Study

If a participant has serious bleeding during the study treatment period that requires hospitalization, the following routine measures should be considered:

- Temporarily or permanently discontinue the randomized study medication. The decision to discontinue study intervention, temporarily or permanently, will be at the discretion of the treating physician and must be documented.
- Temporarily discontinue anti-platelet therapies (i.e. ASA) until the bleeding event is sufficiently controlled, based upon the discretion of the treating physician.
- Investigate other causes of serious bleeding such as coagulopathies, thrombocytopenia, kidney / liver dysfunction, or other concomitant medications.
- Consider usual supportive treatments for bleeding, including local control of bleeding through standard procedures based upon the bleeding location, fluid replacement, blood transfusion, and fresh frozen plasma (FFP) transfusion. Consideration may also be given to the use of an antifibrinolytic agent, such as tranexamic acid or ϵ -amino caproic acid (Tomaselli et al. 2017).

If bleeding cannot be controlled by the above measures, consider urgent surgical or non-surgical procedures to stop the bleeding (emergency surgery, arterial embolization, endoscopic cauterization, etc.) and unblinding of the randomized treatment assignment.

For those participants treated with BAY 2433334, administration of the following procoagulants should also be considered (according to the dosages advised in the package insert):

- Recombinant FVIIa (NovoSeven) or factor eight inhibitor bypass activity (FEIBA), based on vitro data showing that it can fully reverse the prolongation of aPTT and ROTEM CT induced by BAY 2433334.
- FXI concentrate (FXI)

For those participants treated with apixaban, the following agents may be administered:

- The antidote to apixaban, Andexanet alfa, which is a recombinant modified human factor Xa protein (labelled in the US as ANDEXXA and in the EU as Ondexxya), and may be used in case of life-threatening or uncontrolled bleeding ([Steffel et al. 2018](#)). However, its availability may be limited.
- 4-factor Prothrombin complex concentrate (4F-PCC) or Activated prothrombin complex concentrate (APCC)

6.5.2 Guidance for Management of Participants who Have Surgery or Percutaneous / Endoscopic Procedures

When possible, surgery and percutaneous / endoscopic procedures should be planned and delayed for at least 24 hours to allow for a 24-hour washout period after temporary discontinuation of randomized study intervention to mitigate risks of bleeding.

For urgent or emergent surgery or percutaneous / endoscopic procedures, when waiting for 24 hours is not an option to allow for study intervention washout after temporary discontinuation, the increased risks of procedural bleeding should be assessed against the urgency of the procedure based upon the clinical situation. Peri-procedure management may in part, depend on the randomized treatment assignment (BAY 2433334 or apixaban) and unblinding of treatment assignment may be necessary. In general, the treatment recommendations should follow the Guidelines for Severe Perioperative Bleeding Management ([Kozek-Langenecker et al. 2013](#)). The procedure should be conducted in such a way to minimize the risk of bleeding.

Treatment of participants receiving BAY 2433334 during urgent or emergency procedures may be guided by published data regarding patients with an inherited FXI deficiency. Apart from giving FXI concentrate as replacement therapy to cover a surgical bleeding event ([Ling et al. 2016](#)), there have been reports in the literature about the successful use of tranexamic acid or ϵ -amino caproic acid for the management of these patients with an FXI deficiency when undergoing surgery ([Duga and Salomon 2013](#)). More detailed information may be found in the Investigator's Brochure.

Depending on the participant's risk of bleeding with the procedure, participants receiving apixaban who require an invasive or surgical procedure within 24 hours of their last dose may be treated with prophylactic peri-procedural FFP (2 units IV every 6 hours) at the discretion of the local physician and investigator. In addition, the label instructions for apixaban should be followed.

If treatment with an alternative open label anticoagulant / antithrombotic is indicated for the procedure, it should be used at the lowest therapeutic dose (if at all) in the 12 hours following last dose of apixaban. Interactions between apixaban and other antithrombotics (except for aspirin and P2Y₁₂ inhibitors) have not been evaluated.

6.5.3 Guidance for Management of Participants who Experience Ischemic Stroke During the Study

For participants who experience an ischemic stroke during the study, a complete diagnostic work-up including brain imaging, at least 24-hour cardiac rhythm monitoring, and echocardiography is encouraged.

The treatment assignment may have to be emergently unblinded if necessary, to facilitate management decisions (e.g. intravenous thrombolysis or intra-arterial thrombolysis in case of mechanical clot removal).

For participants with acute ischemic stroke who are receiving BAY 2433334, the risk of bleeding with use of intravenous thrombolysis is unknown and has not been studied; hence a clear recommendation in this situation cannot be given. However, it is not recommended that a thrombolytic agent be given unless it is known that the study intervention (BAY 2433334) has not been taken in the previous 48 hours, and the aPTT is normal. In this case, the risk of bleeding associated with thrombolysis is not expected to be increased (and unblinding may not be necessary).

No high-quality data are available regarding the use of intravenous thrombolysis for acute stroke in participants receiving apixaban; therefore, for participants with acute ischemic stroke who are receiving apixaban, the use of thrombolytic agents will follow local practice.

Based on the half-life of apixaban (approximately 12 hours) it may be anticipated that little or no study intervention is present in circulation if the last dose of study intervention was given at least 48 hours before. The anti-Factor Xa chromogenic assay, when used with validated calibrators and controls and where available, may be used to confirm that little or no residual anticoagulant effect is present for participants on apixaban.

For participants who undergo thrombolysis; study medication should be withheld until at least 24 hours after thrombolysis.

Mechanical clot removal (thrombectomy) without thrombolysis may be performed in any case.

6.5.4 Guidance for Management of Participants who Experience new Myocardial Infarction During the Study

For participants who experience a suspected new, acute cardiac ischemic event requiring unplanned hospitalization (unstable angina or acute MI), standard of care medications should be administered according to local practice guidelines and based upon the chosen invasive procedure (dual anti-platelet therapy, if not already being used, intravenous / subcutaneous anticoagulants, or intravenous anti-platelet therapies such as glycoprotein IIb/IIIa inhibitors or cangrelor). Study intervention should be temporarily discontinued upon hospital presentation for a suspected acute or cardiac ischemic event to mitigate potential bleeding risks. Cardiac ischemic event (acute MI) endpoint reporting guidelines and processes should be followed for these situations.

For participants who undergo urgent or emergent coronary angiography (with or without PCI) as treatment for the new ischemic event, study intervention should be restarted no earlier than

24 hours after the arterial sheath has been removed and / or no earlier than 24 hours after the last dose of intravenous / subcutaneous anticoagulant or intravenous anti-platelet agent has been administered. For participants who are treated with urgent or emergent CABG surgery for the new ischemic event after coronary angiography, study intervention should be restarted no earlier than 24 hours after the post-surgical drains (chest tubes) have been removed.

The treatment assignment may have to be emergently unblinded to facilitate decisions regarding treatment with intravenous fibrinolytics for acute ST-elevation MI. For participants who are receiving BAY 2433334 or apixaban, the risk of bleeding related to the concomitant use of an intravenous fibrinolytic is unknown and has not been studied. For participants treated with intravenous fibrinolytics, study intervention should be restarted no earlier than 24 hours after receiving fibrinolytics.

6.6 Dose Modification

This protocol does not allow any alteration from the currently outlined dosing schedule (Section 4.3).

6.7 Intervention after the End of the Study

No further study intervention is planned following the End of the Study. For the definition of “End of Study” please refer to Section 4.4.

Any further therapy at the end of the study is at the discretion of investigator / treating physician.

7. Discontinuation of Study Intervention and Participant Discontinuation / Withdrawal

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for bleeding and efficacy outcome events until the planned regular end of treatment. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

An ET visit is only applicable to participants who prematurely discontinue intake of study intervention; such participants should undergo the ET visit as soon as possible, after permanent discontinuation of study intervention. A safety follow up visit (telephone call) will occur 14 days after the day of the premature discontinuation of study intervention (+ 7 days window). If the ET visit falls into the time window for the safety follow up visit (≥ 2 weeks after permanent discontinuation of study intervention), a safety follow up visit will not be performed.

In this study, outcome events and vital status data are crucial to the primary analysis and must be collected until the end of the study, as participants will still be part of the study even if they are no longer taking study medication. Therefore, all efforts will be taken to motivate participants to comply with all study procedures and to continue to be followed until the end of the study.

Study intervention will not be routinely discontinued in participants reaching a potential outcome event or in case of unblinding, unless there is a safety concern or a clear indication for an alternative antithrombotic therapy as determined by the local investigator.

Specifically, a permanent discontinuation of study interventions will be required if concomitant treatment with any of the following medications has to be taken for the remaining duration of the study:

- chronic anticoagulation for a different indication than AF (e.g. cardiac thrombus, pulmonary embolism)
- chronic antiplatelet therapy (up to 100 mg ASA is allowed as well as ASA and P2Y₁₂ inhibitors in case of a myocardial infarction and / or PCI)
- strong CYP3A4 inhibitors as well as strong CYP3A4 inducers.

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined below, or if the investigator believes that it is in best interest of the participant (please also refer to Section 10.5 for the requirements for liver function monitoring).

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN or INR > 1.5)
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and / or eosinophilia (> 5%)

See the SoA for data to be collected at the time of premature intervention discontinuation and for any further evaluations that need to be completed.

At the time of permanent discontinuation of the study intervention, the participant is expected to continue regular study clinic visits at the investigator's site as outlined in the protocol.

If this is not possible for any reason, the investigator and participant must discuss and determine further follow-up options, as listed below, in descending order of preference:

1. Participant will be contacted by phone at the regular follow-up intervals
2. Participant allows his / her treating physician, e.g. general practitioner or a family member, to be contacted or his medical file checked at the regular follow-up interval, or at least once at study end (if allowed in respective country)
3. Participant will be contacted only once at the planned End of Treatment period (planned regular EOT visit for the participant)

After permanent discontinuation of the study intervention, the following will need to be collected at the regular study visits and up to the regular end of treatment visit, preferentially directly from the participant and as agreed to by the participant during the initial informed consent process:

- Vital Status
- Antiplatelet and anticoagulant medications
- Outcome events (MI, stroke, systemic embolism, death, bleeding).

If a participant is unwilling or unable to return for follow-up visits in person or have follow-up contacts, sites should collect as much follow-up visit information as possible, including

contacting the participant or the participant's representative, family member or treating physician by telephone or by mail. If applicable, vital status may be obtained by reviewing the participant's medical or public sources (e.g. social media, health insurance, public [death] registry), unless this process is not allowed by local regulations.

Withdrawal of Consent

Note: None of the above options is considered a withdrawal of consent.

A withdrawal of consent should only occur in exceptional cases and means that the participant does not agree to any kind of follow-up and specifically refuses any further contact with the investigator (see Section 7.2).

7.1.1 Temporary Discontinuation

In the event of a temporary interruption of study intervention for any reason, study intervention will be restarted as soon as medically justified in the opinion of the investigator. There is no predefined maximum limit for temporary treatment interruption.

If study interventions will be temporarily stopped, PK / PD blood samples should only be obtained if study interventions have been restarted and sustained for at least 4 days.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- At the time of informed consent, participants will be explained all the options to continue in the study after permanent discontinuation of study intervention (see Section 7.1). This will be re-discussed at the time of permanent discontinuation of study intervention and the participant's specific agreement will be documented. Participants will agree to be contacted to obtain follow-up information should they decide to stop the intervention.
- When a participant withdraws consent from study participation before completing the study, meaning that the participant does not agree to any kind of follow-up and specifically refuses any further contact with the investigator, the reason for consent withdrawal is to be documented in the source document. Public information can be used to obtain vital status for these participants where allowed by local regulations.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly (twice) fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow up.
- In order to reduce risk for lost to follow-up the site should collect 2 alternative means of contact for each participant e.g. contact information of family members, caretaker, legal representative, or treating physician. The correctness of these contact details should be checked regularly at the study visits.
- A patient locator service may be used to re-establish contact with a participant in case the site has exhausted all means of regaining contact, if the participant will agree to this in the ICF.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

8.1.1 Exploratory Efficacy Endpoint

No primary or secondary efficacy endpoints are planned to be analyzed in the study. The efficacy endpoints are exploratory endpoints, and include the analysis of composite, as well as individual components, of:

- ischemic stroke
- systemic embolism
- MI
- CV death

In addition, all-cause mortality will be analyzed.

A definition of the efficacy outcome events is provided as follows, and further specified in the charter of the clinical event committee (CEC). Details on the time periods for collecting Outcome Events information are reported in Section 10.9.

8.1.1.1 Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by an injury of the brain, spinal cord, or retina as a result of hemorrhage or infarction.

Differentiation is made regarding ischemic stroke and hemorrhagic stroke.

Hemorrhagic stroke is defined as an acute, atraumatic extravasation of blood into the brain parenchyma, intraventricular or subarachnoid space with associated neurological symptoms. This does not include microbleeds or hemorrhagic transformation of an ischemic stroke.

An ischemic stroke is defined as rapid onset (or presence on awakening) of a new focal neurological deficit with clinical (≥ 24 hours symptoms / signs) or imaging evidence of infarction that is not attributable to a non-ischemic cause (i.e. not associated with infection, tumor, seizure, severe metabolic disease).

The term undetermined stroke will apply when sudden focal neurological deficits persist for 24 hours (or if death occurs before 24 hours) but without neuroimaging or autopsy.

8.1.1.2 Systemic Embolism

Systemic embolism is defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms (this does not include thromboembolism of the pulmonary vasculature or venous thrombosis, e.g. pulmonary embolism or deep venous thrombosis).

8.1.1.3 Myocardial Infarction

The term acute myocardial infarction (MI) is used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. According to the MI Universal Definition from 2018 (Thygesen et al. 2018) the diagnosis of MI requires the combination of:

- Presence of acute myocardial injury (changes in cardiac biomarkers) **and**

- Evidence of acute myocardial ischemia derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging, or in case of post-mortem pathological findings irrespective of biomarker values

8.1.1.4 Cardiovascular Death

Cardiovascular death includes death due to stroke, myocardial infarction, heart failure or cardiogenic shock, sudden death or any other death due to other cardiovascular causes. In addition, death due to non-traumatic hemorrhage will be included.

8.2 Safety Assessments

The safety endpoints are primary, secondary and exploratory endpoints of the study. At each visit during the study as specified in the SoA, the investigator will evaluate the participant for the occurrence of bleeding events. All necessary information to classify bleeding events according to the ISTH, the Thrombolysis In Myocardial Infarction (TIMI) and the Bleeding Academic Research Consortium (BARC) criteria will be collected in the CRF.

8.2.1 Primary Safety Endpoint

The primary safety endpoint includes the analysis of the composite of ISTH major bleeding (Section 8.2.1.1) and clinically relevant non-major bleeding (Section 8.2.1.2).

8.2.1.1 ISTH Major Bleeding

An event that meets at least one of the below criteria for a major bleeding event according to the definition given by the ISTH:

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), and/or
- Clinically overt* bleeding associated with a recent decrease in the hemoglobin level of ≥ 2 g/dL (20 g/L; 1.24 mmol/L) compared to the most recent hemoglobin value available before the event, and/or
- Clinically overt* bleeding leading to transfusion of 2 or more units of packed red blood cells or whole blood

*overt bleeding requires the identification of the bleeding location and the hemoglobin drop and/or transfusion needs to be related to the bleeding

8.2.1.2 ISTH Clinically Relevant Non-Major Bleeding

Clinically relevant non-major bleeding is considered any sign or symptom of hemorrhage that does not fit the criteria for the ISTH definition of major bleeding, but does meet at least one of the following criteria (Kaatz et al. 2015):

- requiring medical intervention by a healthcare professional
- leading to hospitalization or increased level of care
- prompting a face to face (i.e. not just a telephone or electronic communication) evaluation

8.2.2 Secondary Safety Endpoints

The secondary safety endpoints include the analysis of the following outcome events:

- All bleeding
- ISTH major bleeding (Section 8.2.1.1)
- ISTH clinically relevant non-major bleeding (Section 8.2.1.2)
- ISTH minor bleeding (Section 8.2.2.1).

8.2.2.1 ISTH Minor Bleeding

All other overt bleeding episodes not meeting the above criteria for ISTH major or clinically relevant non-major bleeding will be classified as minor bleeding (e.g. bleeding from a minor wound that does not prompt a face-to-face evaluation for a physical examination or laboratory testing).

8.2.3 Exploratory Safety Endpoints

The exploratory safety endpoints include the analysis of the following outcome events:

- TIMI clinically significant bleeding
- TIMI major bleeding
- TIMI minor bleeding
- BARC bleeding definition type 2, 3, 5
- BARC bleeding definition type 3, 5
- BARC bleeding definition type 1, 2, 3, 5

8.2.3.1 TIMI Bleeding Definitions

The non-CABG-related TIMI clinically significant bleeding definition encompasses the following bleeding types excluding events that are related to a CABG procedure:

- **TIMI Major Bleeding**
 - Any symptomatic intracranial hemorrhage
 - Clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of ≥ 5 g/dL (or when the hemoglobin concentration was not available, an absolute drop in hematocrit of $\geq 15\%$).
 - Fatal bleeding (bleeding that directly results in death within 7 days)
- **TIMI Minor Bleeding**
 - Any clinically overt sign of hemorrhage (including imaging) that was associated with a fall in hemoglobin concentration of 3 to < 5 g/dL (or, when hemoglobin concentration was not available, a fall in hematocrit of 10 to $< 15\%$).
- **TIMI Bleeding Events Requiring Medical Attention**
 - Any bleeding event that required medical treatment, surgical treatment, or laboratory evaluation and did not meet criteria for a major or minor bleeding event, as defined above.

In addition to TIMI significant bleeding also TIMI major bleeding and TIMI minor bleeding will be analyzed ([Chesebro et al. 1987](#)).

8.2.3.2 BARC Bleeding Definition

The BARC bleeding definition encompasses the following bleeding types (type 4: CABG-related bleeding is not applicable to this study):

- **Type 0:** no bleeding
- **Type 1:** bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
- **Type 2:** any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
- **Type 3:**
 - Type 3a**
 - Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed)
 - Any transfusion with overt bleeding
 - Type 3b**
 - Overt bleeding plus hemoglobin drop ≥ 5 g/dL* (provided hemoglobin drop is related to bleed)
 - Cardiac tamponade
 - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
 - Bleeding requiring intravenous vasoactive agents
 - Type 3c**
 - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging or lumbar puncture
 - Intraocular bleed compromising vision
- **Type 5:** fatal bleeding
 - Type 5a**
 - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
 - Type 5b**
 - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1g/dL hemoglobin)

8.2.4 Physical Examinations

- Height and weight (also referred to as biometrics in the SoA) will be measured and recorded at screening (see Section 1.3).

8.2.5 Vital Signs

- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure, and pulse

8.2.6 Electrocardiograms

- A single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals.

8.2.7 Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor.
 - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
 - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
 - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

Events identified as Adverse Events of Special Interest (AESI) for the study are specified in Section 8.3.7.

AEs that are outcome events according to the study protocol are further described in Section 8.3.6 and Section 10.3.5.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study intervention and/or study. AESIs have to be followed up regardless of causality or relationship to study intervention.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the start of intervention (first day of study intervention intake) until the safety follow-up visit, at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the start of intervention until the safety follow-up visit, at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History / Current Medical Conditions section of the case report form (CRF), not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours after the investigator becomes aware of this event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he / she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and / or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits / contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements

relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB / IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until 4 days after the last dose intake.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Disease-Related Events

During the study there will be incidences where AEs are also potential efficacy or safety endpoints.

In compliance with applicable regulations, in the event of a SUSAR related to the blinded treatment, the participant's treatment code will usually be unblinded before reporting to the Health Authorities. Notifications of IECs / IRBs and investigators will be done according to all applicable regulations (see Section 8.3.4).

The following disease- and treatment-related events are common in participants with AF who are being treated with an anticoagulant:

- a. Bleeding
- b. Death
- c. Myocardial Infarction
- d. Ischemic stroke
- e. Systemic embolism

These events will be recorded on the corresponding CRF page in the participant's CRF.

These events will also be monitored and adjudicated by a Central Event Committee (CEC) on an ongoing basis.

In addition, these events require reporting to the sponsor according to the standard process of expedited reporting of SAEs within 24 hours of the investigator's awareness of the event, along the timelines set for reporting of SAEs and AESIs.

However, due to their expectedness, efficacy endpoints listed above (b-e: death, myocardial infarction, ischemic stroke and systemic embolism), including events indicative of those

outcome events (e.g. TIA, cardiac chest pain), will not be subject to systematic unblinding and expedited SUSAR reporting to Health Authorities.

8.3.7 Adverse Events of Special Interest

Adverse events of special interest (AESIs) will be AEs related to hepato-biliary dysfunction, i.e. relevant increases in the respective liver lab values (ALT > 3 x ULN or AST > 3 x ULN, with confirmatory re-testing within 5 days of the initial laboratory value elevation) with or without symptoms such as e.g. nausea, vomiting, right upper quadrant abdominal pain, fatigue, weakness, weight loss and jaundice. Re-testing of lab values can be performed at the local lab and needs to be documented in the eCRF.

AESIs have to be reported to the sponsor within 24 hours of the investigator's awareness, i.e. along the timelines set for SAEs (even though they may not be classified as serious), as described in Section 8.3.1.

8.4 Treatment of Overdose

For this study, any dose of BAY 2433334 greater than 3 assigned daily dosages (i.e. more than 6 tablets) within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose of BAY 2433334, as a specific antidote for the study drug is not available. The use of activated charcoal to reduce absorption may be considered.

For participants receiving comparator treatment, and in line with the apixaban label, administration of activated charcoal may be useful in the management of apixaban overdose (i.e. the accidental or intentional ingestion of any dose of apixaban that is considered both excessive and medically important) by leading to a more rapid fall in apixaban blood levels. For further details the investigator / treating physician should refer to the approved product label of apixaban.

Due to the mechanism of action, an overdose of either of the study interventions could potentially result in hemorrhage. In case of bleeding linked to overdose the guidance on bleeding management as found in section 6.5.1 should be followed.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study drug can no longer be detected systemically (at least 5 days.).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 Pharmacokinetics

For the investigation of systemic exposure to BAY 2433334 and its relationship with treatment effects, the plasma concentrations of BAY 2433334 and optionally of its metabolite M-10 (BAY 2826102) will be determined at different time points using a sparse sampling approach in all participating participants. Details about the collection, processing, storage and shipment of samples will be provided separately (e.g. in the Laboratory Manual). Study

personnel responsible for bioanalytics will be unblinded and will have access to the randomization list. Analysis of samples from participants not treated with BAY 2433334 is optional.

Blood samples will be collected at the time points indicated in the SoA (Section 1.3). PK samples obtained at additional time points based on the investigator's discretion will not qualify as a protocol deviation and will be used for PK analysis as well. Deviations from the specified sampling intervals will be documented and taken into account for the PK analysis. Date and time of the PK sample collection and date and time of most recent study intervention intake (i.e. both of the PK/PD sampling day, and of the day before that) must be documented.

At Visit 4 a trough sample for the determination of BAY 2433334 plasma concentrations will be drawn before intake of study intervention. At this visit, study intervention will be administered at the study center by study personnel and the exact time of study intervention intake on the day before the visit and on the day of the visit and the exact sampling time will be recorded in the eCRF. At Visit 6 a plasma sample will be drawn without previous or subsequent study intervention intake; the last intake of study intervention is occurring on the previous day (as usual in the morning and evening). Furthermore, the sampling should occur prior to the intake of an open-label oral anticoagulant (NOAC or another recommended anticoagulant as deemed appropriate by the investigator) that is supposed to be started instead of the blinded study intervention after the end of study intervention treatment. Ideally, the study personnel should contact the participant prior to Visit 4 and Visit 6 to remind them not to take the study intervention as usual in the morning at home. At Visit 4 additional post-dose samples will be taken like indicated in the SoA (Section 1.3).

The PK data and the relationship of the BAY 2433334 exposure parameters (e.g. C_{max} , AUC) with treatment effects might be evaluated using population approaches (e.g. non-linear mixed effect modeling) including potential influence of relevant participant co-variables. Analysis and report will be done under a separate cover. This evaluation might be started prior to database lock: if this is applicable, appropriate measures will be taken to maintain blinding of the study team.

PK samples will be analyzed, using validated analytical methods. Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of calibration samples and QC samples will be reported in the Bioanalytical Report which will be included in the CSR for this study.

8.6 Pharmacodynamics

Blood sampling for PD parameters is scheduled for the time points as given in Section 1.3. The actual date and time of blood sampling will be documented in the CRF. All PD parameters will be measured using validated methods.

Quality control and calibration samples will be analyzed concurrently with study samples. For selected PD parameters, the results of QC samples will be reported together with analyte concentrations in the clinical study report (CSR) of this study.

Concentrations of the analyte are calculated according to the method description. Detailed method descriptions of all PD methods will be filed with the study report.

The following parameters will be used to assess the PD effects after administration of the investigational drug, but will be performed optionally and/or only in a subset of participants:

- aPTT will be measured using a coagulation assay via kaolin-trigger

- Activated Factor XIa activity (AXIA) will be analyzed using a kaolin-trigger and a fluorogenic substrate readout.
- D-Dimer will be measured using an immunoturbidometric method
- FXI concentration will be measured via ELISA using polyclonal antibodies
- Fibrinogen will be measured using a coagulation assay
- Factor XII activity will be assessed with an aPTT-based coagulation test using FXII-deficient plasma. Factor XII concentration will be analyzed using an enzyme-linked immunosorbent assay (ELISA).
- vWF antigen level and vWF ristocetin cofactor (i.e. vWF functional activity) will be analyzed using turbidometric assays.

The study sponsors reserve the right not to conduct all or part of the above-mentioned analysis.

In addition, blood samples will be taken for exploratory biomarker work (see Section 8.8).

Detailed information about the collection, processing, storage and shipment of the samples will be provided separately (e.g. sample handling sheets and/or laboratory manual).

8.7 Genetics

Genetic as well as non-genetic analyses will be part of the biomarker investigations in this study. See Section 8.8 for details.

8.8 Biomarkers

Exploratory biomarker analyses (scheduled for the time points as given in Section 1.3), that might be performed optionally and/or only in a subset of participants are:

- NT-proBNP will be measured using an electrochemiluminescence immunoassay (ECLIA)
- hsCRP will be measured using an immunoturbidometric method
- Thrombin-activatable fibrinolysis inhibitor (TAFI) and C1 inhibitor activity will be measured using chromogenic substrate assays
- TAT and F1.2 will be analyzed using immunoassays

In addition to the biomarkers described above, further biomarkers related to the mode of action or the safety of BAY 2433334 and similar drugs may be examined. The same applies to further biomarkers deemed relevant to cardiovascular diseases and associated health problems. These investigations may include e.g. diagnostic, safety, PD, monitoring, or potentially predictive biomarkers.

Those additional analyses may include genetic as well as non-genetic biomarkers. Genetic investigations may be of any kind, except for whole genome sequencing. Results will be reported under separate cover, if the evaluations are performed.

Details on the collection, processing, storage, and shipment of biomarker samples will be provided in separate documents (e.g. sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.

8.9 Immunogenicity Assessment

Not applicable

8.10 Health Economics / Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1 Statistical Hypotheses

The aim of the study is to estimate the incidence risk of bleeding events of BAY 2433334 and compare it with the incidence risk of apixaban.

No hypothesis testing is planned in this study.

9.2 Sample Size Determination

Approximately 800 participants will be screened to achieve 750 evaluable participants for an estimated total of 250 evaluable participants per intervention group.

The bleeding risk for the 2 dose groups of BAY 2433334 is assumed to be similar, such that pooling of the BAY 2433334 arms will be done for the bleeding comparison. The precision of the estimated incidence risks (measured by the length of the confidence interval) depends on both the observed incidence risk and the relative risk reduction. For an observed incidence risk for the primary bleeding endpoint of 4% at Week 12 in the apixaban control arm and an observed relative risk reduction of 50% for both (mid and high) doses of BAY 2433334, sample sizes of 250 (apixaban) and 500 (pooled BAY 2433334 arms) participants produce a two-sided 90% confidence interval for the ratio of incidence proportions with a length of 0.77 (0.25- 1.02). In this case the expected number of bleeding events in the apixaban control arm is 10 and 5 in each of the BAY 2433334 treatment arms. Further calculations for exemplary approximate two-sided 90% confidence intervals and their lengths for different observed incidence ratios and relative risk reductions are presented in [Table 9–1](#), below.

Table 9–1: 90% Confidence Intervals for the ratio of incidence and the corresponding length for different scenarios at week 12

Observed Relative Risk Reduction under BAY 2433334 treatment	Observed incidence in comparator arm			
	3%	4%	5%	6.5%
45%	0.25 – 1.22 (0.97)	0.28 – 1.10 (0.82)	0.31 – 1.02 (0.72)	0.32 – 0.95 (0.63)
50%	0.22 – 1.13 (0.91)	0.25 – 1.02 (0.77)	0.27 – 0.95 (0.68)	0.29 – 0.88 (0.59)
55%	0.19 – 1.04 (0.85)	0.22 – 0.93 (0.71)	0.24 – 0.86 (0.64)	0.25 – 0.80 (0.55)

Given the assumptions of a true incidence rate for apixaban of 4% for the primary safety endpoint and a true relative risk reduction of 50% the point estimator will be lower than or equal to 0.72 with a probability of 80%, lower than or equal to 0.88 with a probability of 90% and lower than or equal to 1 with a probability of 94%.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Full Analysis Set	All participants randomized to study intervention.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis Set	All BAY 2433334-treated participants with at least 1 valid plasma concentration and without protocol deviation, which would interfere with the evaluation of the PK data.

Abbreviations: ICF = Informed consent form, PK = pharmacokinetic(s)

The primary and secondary safety endpoints will be analyzed using the Safety Set. The analysis of the Full Analysis Set (FAS) will be used as a supportive analysis. Pharmacokinetic and pharmacodynamic data will be analyzed using the Pharmacokinetic analyses set.

9.4 Statistical Analyses

9.4.1 General considerations

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints and estimands.

The aim of this study is to gain knowledge of the safety profile of BAY 2433334.

For the intercurrent events “death” and “discontinuation of study treatment” the “while on treatment” respectively “while alive” strategy will be applied, if not mentioned otherwise, i.e. only data up to the respective intercurrent event will be considered for the analysis.

Confidence intervals will be two sided 90% - confidence intervals.

The cumulative incidence risk will be estimated for time to event endpoints. The hazard ratios and the corresponding confidence intervals will be estimated on separate Cox proportional hazard models for each comparison. No comparison of the different doses of BAY 2433334 is planned.

All collected events will be summarized using methods like frequency tables and descriptive statistics.

The statistical analyses will be performed using SAS; the version used will be specified in the SAP.

9.4.2 Primary endpoints

Safety Analysis

The primary estimand is the ratio of proportion of participants experiencing the composite of ISTH major and clinically relevant non-major bleeding within 3 months comparing pooled doses of BAY 2433334 and apixaban, the comparator drug, in adult participants with AF who have taken at least one dose of study intervention (BAY 2433334 or apixaban), while the participant is alive and exposed to study intervention.

The primary estimator is a confidence interval for the ratio of incidence risks, accounted for the participants under risk, of BAY 2433334 (all doses pooled) and the active comparator. The estimation will be performed on the safety set.

For the “while on treatment” respectively the “while alive” strategy all events from first intake of study intervention until 2 days after last study intervention intake will be counted. A supplementary estimand will use the “treatment policy” strategy for the intercurrent event “discontinuation of study intervention” and change the population to all participants randomized to a study intervention. It will be estimated on the ITT data set, and all events from randomization through the safety follow-up visit will be counted and displayed for the pooled doses of BAY 2433334, as well as for the individual doses.

As supplementary analysis, the primary safety endpoint will be analyzed as time to event variable. The comparison will be done for each dose of BAY 2433334 vs. the active comparator as well as for the pooled doses of BAY 2433334.

All analyses will be stratified based on whether participants received a NOAC before study start or were not treated with any other oral anticoagulant.

9.4.3 Secondary endpoints

Safety Analyses

The secondary safety estimands are the ratios of the proportions of participants experiencing the individual endpoints within 3 months, comparing pooled doses of BAY 2433334 and comparator drug apixaban in adult participants with AF who have taken at least one dose of study intervention (BAY 2433334 or apixaban, the comparator drug), while the participant is alive and exposed to study intervention for each of the endpoints:

- all bleeding
- ISTH major bleeding
- ISTH clinically relevant non-major bleeding
- ISTH minor bleeding.

The analyses will be similar to those for the primary safety endpoint.

9.4.4 Tertiary / exploratory endpoints

Exploratory endpoints for this study are the composite as well as individual components of CV death, MI, ischemic stroke, systemic embolism and all-cause mortality as efficacy endpoints; TIMI clinically significant bleeding, TIMI major bleeding, TIMI minor bleeding, BARC bleeding definition type 2, 3, 5, BARC bleeding definition type 3, 5 and BARC bleeding definition type 1, 2, 3, 5 as safety endpoints and FXIa inhibition, aPTT, D-Dimer and various biomarkers (e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers) as other endpoints.

The analyses of these endpoints will be specified in the SAP.

9.4.5 Other safety Analyses

Adverse Events (AE) will be analyzed by descriptive statistics, such as frequency tables. All AEs will be tabulated according to the affected system organ class and preferred term, as coded by the Medical Dictionary for Regulatory Activities (MedDRA).

9.4.6 Other Analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the CSR.

9.5 Interim Analyses

No formal interim analysis is planned for this study.

Two non-formal interim analyses are planned to be performed in the Phase 2 program to assess the efficacy and safety profile of BAY 2433334 during the Phase 2 study conduct. Data from this study as well as the 2 other ongoing Phase 2 studies will be reviewed together when the pre-defined criteria for the 2 interim analyses have been reached.

Analyses of the unblinded safety and efficacy data will be performed by a third party, i.e. the statistical analysis center (SAC) that supports the IDMC and thus, is independent of the study team and the sponsor. A small group of academic leaders (Executive Committee) including the heads of the three Steering Committees that have been established for the individual studies and sponsor representatives will participate in the review of these data. IDMC members will also be included in this review. The data will be kept strictly confidential by this group and will not be shared with the study team and the SC. Thus, the study integrity will not be impacted and the study conduct will otherwise not be altered by the results of this interim analysis.

The interim analysis will include selected and predefined study data primarily as aggregated data for this individual study but may also include pooling of some data across all 3 ongoing Phase 2 studies.

The first interim analysis will be conducted once about 50% of the participants (800 participants) with a minor non-cardioembolic ischemic stroke ($\text{NIHSS} \leq 7$) are enrolled in the study 19766, or 3 months MRI data are available for at least 12.5% of participants (200 participants). If the review confirms the safety profile of BAY 2433334 and raises no concern regarding (intracranial) hemorrhage or hemorrhagic transformation of the ischemic stroke, Part B of the study 19766 will be initiated, during which from then on participants with more severe cases of stroke ($\text{NIHSS} \geq 8$ and ≤ 15) can also be included as well as participants after thrombolysis or endovascular therapy (mechanical thrombectomy). Even though the primary focus for this interim analysis is specific for the decision for the stroke study only, data and especially bleeding data from the other 2 studies will be taken into consideration.

The second interim analysis will occur, when approximately 80% of all planned participants, taken all 3 studies together, are randomized. This meeting will aim to assess whether the interim data support decision making on dose and design for a potential Phase 3 clinical development program while the Phase 2 studies are still ongoing and may allow interaction with Health Authorities before final data from the studies are available.

The timepoints when these two interim analyses occur are difficult to predict and will depend e.g. on study start time, number of sites and countries, on the enrollment rate and other factors in all three studies. In case the timepoints for the 2 interim analyses may be close together, the decision could be taken to just conduct one interim analysis.

As part of the 2 interim analyses the additional objective to potentially change the dose during the ongoing Phase 2 studies will be assessed. This will allow flexibility in case of unexpected

findings during the review of the data, e.g. stop of the highest dose (in case of an unexpected higher bleeding rate in the highest dose or in the combination with antiplatelet therapy) or addition of a lower or higher dose or replacement of one dose (in case of a difference in pharmacokinetics or PD parameters such as inhibition of FXIa in the patient populations compared to healthy volunteers).

9.6 Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) will be involved in the review of the safety data for study 19765, and of the overall safety data across all 3 Phase 2 studies with BAY 2433334 (Section 10.1.5.3). Detailed information on the roles and responsibilities of the IDMC will be described in the IDMC Charter.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH Good Clinical Practice (GCP) Guidelines
 - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB / IEC by the investigator and to the appropriate regulatory authority by the sponsor. The submitted documents should be reviewed and approved by the IRB / IEC and regulatory authority before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modifications of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- The investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB / IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB / IEC
 - Notifying the IRB / IEC of SAEs or other significant safety findings as required by IRB / IEC procedures
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB / IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB / IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Pharmacogenetic samples will be taken during the study. Study participants will be asked to sign a separate informed consent for pharmacogenetic research.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

10.1.5.1 Executive Committee

The Executive Committee, which consists of external experts in the area of neurology and cardiology and will include the Steering Committee heads of the 3 Phase 2 studies with BAY 2433334, as well as 2 sponsor representatives, will ensure the overarching integrity of the 3 studies. Details of the committee will be specified in the Executive Committee Charter.

10.1.5.2 Steering Committee (SC)

The main task of the Steering Committee, which is composed of a panel of experts in the field cardiology and neurology, is to support the protocol development and the conduct of the study, to advise the sponsor on clinical, medical, and scientific questions, and to support publications. Details of the committee will be specified in the Steering Committee charter.

10.1.5.3 IDMC

Ongoing safety monitoring during the conduct of the study will be performed by an external and unblinded IDMC. An independent statistical analysis center (SAC) will be involved in processing unblinded safety data for the IDMC. Analysis periods and procedures will be defined in an operational charter (IDMC Charter) filed in the study file. Following data review, the IDMC will provide written recommendations that will be transferred to Bayer. All other definitions will be provided in the IDMC charter.

10.1.5.4 Clinical Events Committee (CEC)

Potential pre-specified clinical outcome events will be submitted for adjudication to an independent CEC. Adjudication of all bleeding events as well as potential exploratory efficacy events will be performed by members of the CEC who will review events in a blinded fashion and will adjudicate and classify the following events in a consistent and unbiased manner according to definitions contained in the CEC charter. The adjudication will also include algorithm approaches:

- Bleeding events according to the following classifications:
 - ISTH (major, clinically relevant non-major and minor)
 - TIMI (major, minor, requiring medical attention, minimal)
 - BARC (type 1, 2, 3, 5)
- Death (CV death [including death with unknown cause] or non-CV death)
- MI
- Stroke (ischemic, hemorrhagic, undetermined)
- Systemic embolism

In addition, events that might be indicative of a potential outcome event will be reported as outcome events to ensure that no outcome event is missed. This includes for example TIA and hospitalization for cardiac chest and with increased cardiac enzymes reported.

Data entry procedures and documentation necessary for case adjudication will also be described in the CEC charter. Adjudication results will be the basis for the final analysis.

10.1.6 Dissemination of Clinical Study Data

Result summaries of Bayer's sponsored clinical studies in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in participants for medicines and indications approved in the United States (US) and European Union (EU) on or after 01 JAN 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB / IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor.

No records may be transferred to another location or party without written notification to the sponsor.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

10.1.7.1 Data Recording

The data collection tool for this study will be a validated electronic data capture system called RAVE. Participant data necessary for analysis and reporting will be entered / transmitted into a validated database or data system (LSH).

Data required according to this protocol will be recorded by study site personnel via data entry into the internet-based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all participants enrolled in this study.

Data recorded from screening failures

At minimum, the following data should be recorded in the CRF:

- Demographic information (participant number; year of birth/age; sex; if applicable race / ethnicity)
- Date of informed consent
- Relevant inclusion/exclusion criteria
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

10.1.7.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of participants are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.1.7.3 Data processing

Data will be collected as described in Section 10.1.7.1. Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g. IxRS, laboratory, adjudication committees).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

After its initial release for biometrical analysis, additional data release for analysis is possible, to include, for example, the following data: pharmacokinetic data, pharmacodynamic data, anti-drug antibody data etc.

10.1.7.4 Missing data

All efforts will be made to collect complete data for all participants randomized in this study. Participants will be followed up to the study end and all required data will be collected, regardless of participants' compliance with study intervention use or the visit schedule.

Data from participants who prematurely terminate the study will be used to the maximum extent possible. All missing or partial data will be presented in the participant data listing as they are recorded in the eCRF. Data are collected primarily through an EDC system, which allows ongoing data entry and monitoring.

10.1.7.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

10.1.7.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Participant (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study site.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the source data identification checklist.
- The site must implement processes to ensure availability of all required source documentation (e.g. participant file, local laboratory report, etc.). A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.
- Race and ethnic group may be entered directly into the CRF, without availability of corresponding source documentation. Thus, these CRF data will be the source and no additional source documentation will be available. For all other data, source documentation must be available at the site.

10.1.9 Study and Site Start and Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB / IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Steering Committee as well as the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor and the Steering Committee will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 10–1](#) will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Section 4.4](#) of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10–1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count	<u>RBC Indices:</u>	<u>White blood cell (WBC) count with Differential:</u>
	Red blood cell (RBC) count	MCV	Neutrophils
	Hemoglobin	MCH	Lymphocytes
	Hematocrit	%Reticulocytes	Monocytes Eosinophils Basophils
Clinical Chemistry ^a	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (AP) Gamma glutamyl transpeptidase (γGT) Bilirubin, total and direct		
	Lactate dehydrogenase (LDH) Creatinine kinase (CK)		
	Blood urea nitrogen (BUN) Creatinine eGFR		
	Lipase Amylase		
	Sodium Potassium Calcium		
	Uric acid Glucose Cholesterol (total, HDL, LDL) Triglycerides Albumin Total protein Thyroid-stimulating hormone (TSH)		

Abbreviations: ALT = alanine aminotransferase, AP = alkaline phosphatase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CK = creatinine kinase, eGFR = estimated glomerular filtration rate, γGT = gamma glutamyl transpeptidase, HDL = high-density lipoprotein, LDH = lactate dehydrogenase, LDL = low-density lipoprotein, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, RBC = red blood cell (count), TSH = thyroid-stimulating hormone, WBC = white blood cell (count)

^a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.5.

Investigators must document their review of each laboratory safety report.

The name and address for the central laboratory service provider can be found in the documentation supplied by the vendor. In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

All exploratory biomarkers are not used routinely in practice and will be analyzed in batches. Therefore, timely reporting of the results will not be possible during the study and review of the results will not assist participant care.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs / symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:**a. Results in death****b. Is life-threatening**

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
 - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
-

10.3.3 Recording and Follow-Up of AE and / or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
 - The investigator will then record all relevant AE/SAE information in the CRF.
 - It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE CRF page.
 - There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
 - The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
-

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
 - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
 - Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
 - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category
-

utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
-

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
 - If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any *post mortem* findings including histopathology.
 - New or updated information will be recorded in the originally completed CRF.
 - The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.
-

10.3.4 Reporting of SAEs

SAE Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form and transmit to PPD [REDACTED]
- Contacts for SAE reporting can be found in the Investigator Site File.

SAE Reporting to the sponsor via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor via PPD [REDACTED]
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Site File.

10.3.5 Outcome Event Reporting Process Overview

If an AE or SAE is a potential outcome event (all bleeding, death, MI, stroke, TIA and systemic embolism [Section 8.3.6]), it must be collected and reported on the dedicated forms on an ongoing basis, until the participant has completed the study. Thus, even if a participant is no longer taking study medication this would be until the end of the regular, planned end of treatment for this participant (i.e. until the participant's last visit). After completion of safety follow-up visit, for participants that prematurely discontinued study intervention, there is no further requirement for reporting AEs. Only potential outcome events are to be reported (refer to Section 8.3.1 and Section 10.9).

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (e.g. Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal Female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (> 40 IU/L) is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

- Female participants must be of non-child bearing potential as per Clinical Trial Facilitation Group (CTFG) guidelines.
- Male participants must agree to use condoms when sexually active with a woman of childbearing potential from the time of the first dose to 7 days after the last dose of study intervention. This is in line with the CTFG guideline, as BAY 2433334 is non genotoxic but data related to teratogenicity/fetotoxicity in early pregnancy (Segment 2

studies) are not available at this stage of development. In addition, all men must not donate sperm during the study.

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
 - While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE
 - A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Any participant with an ALT or AST > 3 x ULN must be re-tested as soon as possible, at the latest within 48-72 hours of the investigator becoming aware of the result. This re-testing and any subsequent testing based on elevated levels should include measurement of ALT, AST,

total and direct bilirubin, AP and INR, and will be assessed by local laboratory. There also should be inquiry made about symptoms.

Every effort should be made to clarify the etiology of elevated levels and laboratory testing may include, but not be limited to, testing for viral hepatitis, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus (once the participant has provided written consent), ferritin levels, iron, iron binding capacity, antinuclear antibody, and smooth muscle antibodies. Participant management is at the discretion of the treating physician, but the investigator may continue the study intervention during retesting.

Liver function test monitoring should be performed as above for all participants with elevated ALT or AST >3 ULN even if the study intervention is interrupted until tested values have normalized or returned to participant's baseline. If close liver monitoring is not possible, then the participant should discontinue study medication.

For ALT or AST > 3 x ULN concurrent with a total bilirubin > 2 x ULN, every effort should be made to promptly clarify any possible underlying disease(s).

The frequency of liver function tests based on re-test values is shown in [Table 10–2](#).

Table 10–2: Liver function monitoring

ALT, AST level at re-test	Frequency	Further notice
ALT or AST > 3 x ULN	2-3 times a week	Obtain details on liver related symptoms and exclude other causes of liver enzyme elevations
ALT or AST ≤ 3 x ULN	Once a week	Until return to normal or participant baseline levels

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase; ULN = upper limit of normal

Discontinuation of treatment should be considered if:

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN **and** (total bilirubin > 2 x ULN **or** INR > 1.5)
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$).

10.6 Appendix 6: Calculating the Child-Pugh score

The severity of liver disease ([Table 10–3](#)) will determine the Child-Pugh score ([Table 10–4](#)).

Table 10–3: Grading of severity of liver disease

Factor	+1	+2	+3
Bilirubin (mg/dL)	< 2	2 – 3	> 3
Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
International Normalized Ratio	< 1.7	1.7 – 2.3	> 2.3
Ascites	None	Mild	Moderate/Severe
Encephalopathy	None	Grade I – II	Grade III – IV

Source: adapted from ([Pugh et al. 1973](#))

Table 10–4: Child-Pugh score

Child-Pugh Class	A	B	C
Points	5 – 6	7 – 9	10 – 15

Source: adapted from ([Pugh et al. 1973](#))

10.7 Appendix 7: Calculating glomerular filtration rate

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated glomerular filtration rate (eGFR), calculated using the Modification of Diet in Renal Disease (MDRD) study abbreviated formula.

Isotope dilution mass spectroscopy (IDMS)-traceable MDRD Study Equation:

Conventional units (serum creatinine level is measured in mg/dL)

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

GFR can be estimated using the calculator provided in the following link:

http://www.kidney.org/professionals/kdoqi/gfr_calculator.

For further information on assessing renal function using GFR estimates ([Levey et al. 2006](#)).

10.8 Appendix 8: Calculating CHA₂DS₂-VASc score

Table 10–5: CHA₂DS₂-VASc score

Letter	Risk factor	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A ₂	Age ≥ 75	2
D	Diabetes mellitus	1
S ₂	Stroke/TIA/thromboembolism	2
V	Vascular disease ^a	1
A	Age 65-74	1
Sc	Sex category (i.e. female sex) ^b	1

Abbreviations: AF = atrial fibrillation, LV = left ventricular, TIA = transient ischemic attack

Congestive heart failure/LV dysfunction means LV ejection fraction ≤ 40%.

Hypertension includes the participants with current antihypertensive medication.

^aPrior myocardial infarction, peripheral artery disease, aortic plaque.

Source: adapted from (Lip et al. 2010).

^bRecent studies have suggested that female sex, in the absence of other AF risk factors (CHA₂DS₂-VASc score of 0 in males and 1 in females), carries a low stroke risk that is similar to males. The excess risk for females was especially evident among those with ≥ 2 non-sex-related stroke risk factors; thus, female sex is a risk modifier and is age dependent. Adding female sex to the CHA₂DS₂-VASc score matters for age > 65 years or ≥ 2 non-sex-related stroke risk factors (January et al. 2019).

10.9 Appendix 9: Outcome Events: Data Collection

All outcome events (efficacy and safety) are to be captured and reported from randomization until participant's regular last scheduled study visits (i.e. safety follow-up visit; in case of permanent discontinuation of study intervention, the planned regular EOT visit). The eCRF will contain specific Outcome Event pages, as well as AEs subpages to capture the outcome events occurring throughout the study. The following points need to be considered when reporting outcome events.

- Outcome events occurring **after randomization and before the first intake of the study intervention**: the outcome event will be considered part of the medical history and should be reported in the outcome event eCRF page
- Outcome events occurring **after randomization and after first intake of study intervention and up to the SFU visit**: the outcome event will be considered both AE and outcome event and should be reported in both in the AE page and in the AEs subpage for outcome events.
- Outcome events occurring **after SFU visit through the end of the study (for participant who discontinue study intervention)**: the outcome events should be collected until completion of participant's regular scheduled study visits and should be reported in the outcome event eCRF page.

10.10 Appendix 10: Abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
ACC	American College of Cardiology

AF	Atrial fibrillation
AG	Joint stock company, <i>Aktiengesellschaft</i>
AHA	American Heart Association
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
AP	Alkaline phosphatase
APCC	Activated prothrombin complex concentrate
aPTT	Activated partial thromboplastin time
ARC	Academic Research Consortium
ASA	Acetylsalicylic acid
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
AUC	Area under the curve
AXIA	Activated Factor XIa activity
AxMP	Auxiliary medicinal product
BARC	Bleeding Academic Research Consortium
BID	Twice a day, <i>Bis in die</i>
BL	Baseline
BMS	Bristol-Myers Squibb
BP	Blood pressure
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHEST	American College of Chest Physicians
CIOMS	Council for International Organizations of Medical Sciences
CHMP	Committee for Medicinal Products for Human Use
CK	Creatinine kinase
CL/F	Apparent oral plasma clearance
C _{max}	maximum observed concentration reached after administration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CSR	Clinical study report
CT	Clotting time
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
e.g.	For example, <i>exempli gratia</i>
ECG	Electrocardiogram
ECLIA	Electrochemiluminescence Immunoassay
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of Treatment
ESC	European Society of Cardiology

ESUS	Embolic stroke of undetermined source
ET	Early termination
EU	European Union
EudraCT	European Clinical Trials Database
F1.2	F1.2 fragment of prothrombin
FAS	Full Analysis Set
FeCl	Ferric chloride
FEIBA	Factor eight inhibitor bypass activity
FiM	first in man
FFP	Fresh frozen plasma
4F-PCC	4-factor Prothrombin complex concentrate
FSH	Follicle stimulating hormone
γ GT	Gamma glutamyl transpeptidase
GCP	Good Clinical Practice
geoCV	Geometric coefficient of variation
GFR	Glomerular filtration rate
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HDL	High-density lipoprotein
HDPE	High-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
HRS	Heart Rhythm Society
HRT	Hormonal replacement therapy
hsCRP	High-sensitivity C-reactive protein
i.e.	That is, <i>id est</i>
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent data monitoring committee
IDMS	Isotope dilution mass spectroscopy
IEC	Independent Ethics Committee
IMP	Investigational medical product
IND	Investigational New Drug
INN	International non-proprietary name
INR	International normalized ratio
ISTH	International Society on Thrombosis and Hemostasis
IR	Immediate-release
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Hemostasis
ITT	Intent-to-treat
IV	Intravenous(ly)
IVRS/IWRS, IxRS	Interactive Voice/Web Response System
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LSH	Life Science Data Hub
LV	Left ventricular

MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MD	Medical doctor
MD/MDE	Multiple dose/multiple dose escalation
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
N	Total number of participants
NA	Not applicable
NIHSS	National Institutes of Health Stroke Scale
NJ	New Jersey
NOAC	Non-Vitamin K oral anticoagulant
NSAID	Nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
OD	Once a day
P2Y ₁₂	G _i -coupled platelet receptor for adenosine diphosphate
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Prothrombin time
QC	Quality control
R _A AUC	Accumulation ratio for AUC
R _A C _{max}	Accumulation ratio for C _{max}
RAVE	Data collection tool
RBC	Red blood cell (count)
RND	Randomization
ROTEM	Rotational thromboelastometry
SAC	Statistical analysis center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical analysis software
SC	Steering Committee
SCR	Screening
SD	Single dose
SFU	Safety follow-up
SMOL	Small molecule
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
TAFI	Thrombin-activatable fibrinolysis inhibitor
TAT	Thrombin-antithrombin complex
TIA	Transient ischemic attack
TIMI	Thrombolysis in myocardial infarction
TKA	Total knee arthroplasty
TM	Trademark
t _{max}	Time to reach maximum drug concentration in plasma
TMF	Trial Master File

TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US/USA	United States/United States of America
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
vWF	Von Willebrand Factor
W	Week
WBC	White blood cell (count)
WOCBP	Woman of Childbearing Potential

11. References

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